Am J Transl Res 2026;18(5):3901-3915
www.ajtr.org /ISSN:1943-8141/AJTR0172406

Review Article

Perioperative gut microbiota homeostasis and its interactions with anesthetic agents: recent advances

Xinyang Liu[1], Yuan Xu[2], Jiaru Yu[1]

[1]*Department of Anesthesiology, The Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, Zhejiang, China;* [2]*Operating Room, The Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, Zhejiang, China*

Received March 3, 2026; Accepted April 7, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: The perioperative period is a critical and acute phase during which host-microbiota interactions play an essential role in determining susceptibility to anesthetic exposure and post-surgical stress. Immune homeostasis, gut barrier integrity, and metabolic regulation, as well as gut-brain and gut-liver axis, are highly dependent on the gut microbiota. However, this microbial ecosystem is disrupted during the perioperative period due to the combined effects of fasting, bowel preparation, surgical stress, hemodynamic alterations, and antibiotic and opioid use. Growing evidence has linked perioperative dysbiosis to a wide range of adverse outcomes, including infectious complications, anastomotic leakage, postoperative ileus, organ dysfunction, and perioperative neurocognitive disorders. Meanwhile, anesthetic and analgesic agents do not act in isolation from this ecosystem; rather, they engage in a bidirectional chemical interaction with the microbiota. These interactions can alter microbial structure and metabolite profiles, thereby influencing host metabolic processes, while microbial activity, in turn, affects drug disposition, immune response, and neuroinflammation. In this review, we first describe the vulnerability of gut microbiota homeostasis during the perioperative period and its associated clinical consequences. We subsequently elaborate on the mechanistic framework of anesthetic-microbiota crosstalk, highlighting pathways involving vascular, epithelial, immune and neural signaling. Then, we summarize emerging evidence demonstrating that different anesthetic and analgesic regimens generate discrete microbiota-metabolite signatures, which may underlie intersubject differences in postoperative recovery trajectories. Finally, we describe perioperative microbiota-targeted strategies, including probiotics and synbiotics, postbiotics and microbial consortia, nutritional optimization, and microbiome-based customization of anesthetic and analgesic protocols. Collectively, existing data suggest that preserving and actively modulating gut microbiota homeostasis represents a promising yet underexplored strategy for improving the safety of anesthesia and postoperative outcomes.

Keywords: Perioperative period, gut microbiota, anesthetic agents, microbiota-drug interactions, homeostasis

Introduction

Nowadays, perioperative medicine is increasingly recognized as a critical period during which host physiology is highly susceptible to external stimuli, and the intestinal microbiota is no exception. The intestinal microbiome system plays essential roles in immune homeostasis, metabolic regulation, intestinal mucosal stability, and neuroendocrine communication through the gut-brain and gut-liver axes [1, 2]. Perioperative factors, including surgical stress, fasting, bowel preparation, hemodynamic fluctuations, opioid use, antibiotic exposure, and nutrition alteration, destabilize this ecosystem, particularly in vulnerable patients.

A growing body of clinical and experimental evidence indicates that perioperative dysbiosis, characterized by reduced microbial diversity, expansion of pathobionts, and impaired barrier function, is not merely an epiphenomenon but also linked to a wide range of negative outcomes, such as postoperative ileus, anastomotic leakage, infectious complications, and delayed recovery [3-5]. Simultaneously, the gut-brain axis has been implicated as a key mechanistic link between microbiota disturbances and perioperative neurocognitive disorders such as delirium, especially in elderly or cognitively frail patients [6-8]. Collectively, these findings position the maintenance or targeted modulation of gut microbiota homeosta-

https://doi.org/10.62347/BRJW7664

sis as a potentially modifiable risk factor in perioperative risk.

Within this complex environment, the traditional view of anesthetic agents as mere modulators of hemodynamics and neural activity has been challenged. Emerging evidence indicates that anesthetics not only influence, but are also influenced by, the gut microbiota. Both volatile anesthetics (e.g., sevoflurane) and intravenous agents (e.g., propofol) can induced rapid and sustained alterations in microbial composition, metabolite profiles, and intestinal barrier function, with downstream effects on neuroinflammation and cognitive outcomes [9, 10]. Early clinical evidence further suggests that various anesthetic regimens are associated with distinct microbiota signatures, and that combination strategies may attenuate microbiota perturbations compared with the single-agent approaches [11].

Meanwhile, anesthetic-induced immune dysregulation may be aggravated by microbiota-mediated inflammasome activation and systemic inflammation, thereby increasing the risk of infectious and inflammatory complications [12, 13]. Conversely, the gut microbiota can modulate the pharmacokinetics and pharmacodynamics of anesthetic drugs and opioids through drug biotransformation, hepatic and immune pathway modulation and gut-brain axis regulation. These interactions may contribute to interindividual variability in anesthetic response, analgesic efficacy, and postoperative recovery [14]. Taken together, this bidirectional interaction suggests that anesthetic selection and dosing strategies can be optimized not just for conventional endpoints but also for the preservation of microbiota homeostasis.

Despite these advancements, the field remains fragmented, with significant knowledge gaps limiting translation into perioperative practice. Most available studies are small in scale, heterogenous in design, and vary greatly in patient populations, microbiome profiling techniques, and perioperative co-interventions, making it difficult to separate the specific effects of anesthetic exposure from those of surgical trauma and other confounding factors [15]. Although mechanistic studies are expanding, efforts to systematically map signaling pathways, including microbially-derived metabolites, pattern-recognition receptor activation, inflammasome signaling, and neuroimmune circuits, and to link these pathways to clinically meaningful outcomes such as infection, organ dysfunction, and neurocognitive decline remain in their early stages [16, 17]. Interventional trials focusing on the perioperative microbiota, such as probiotics or prebiotics, diet modulation or fecal microbiota transplantation, are limited and rarely account for anesthetic exposure as a controlled factor. Against this background, this review summarizes current advances at the interface between perioperative gut microbiota homeostasis and anesthetic pharmacology. First, we outlined the impact of surgery and the perioperative environment on the gut ecosystem, followed by discussion of the experimental and clinical data supporting the effects of anesthetics on the microbiota and its metabolites. Subsequently, we elucidated the influence of baseline microbiota composition on anesthetic response and postoperative outcomes. Finally, from the perspective of microbiota-informed anesthetic decisions-making, we highlight conceptual frameworks and translational opportunities for optimizing perioperative care.

Fragility of perioperative gut microbiota homeostasis and clinical implications

In health adults, gut microbiota remains relatively stable over time, yet it is highly sensitive to environmental and physiological stressors [18, 19]. The perioperative period represents a convergence of such stressors, including fasting, bowel preparation, sudden dietary change, surgical trauma, hemodynamic fluctuations, opioid use, and antibiotic exposure, all of which can transform a balanced microbial ecosystem into a dysregulated state. Evidence from gastrointestinal and hepatobiliary surgery, as well as perioperative anesthesia research, indicates that even transient disruptions may result in significant reductions in microbial diversity, expansion of opportunistic pathobionts, and disturbed barrier functions, with downstream effects on immune, metabolic, and neuroendocrine pathways [20]. In susceptible populations, such as older adults and patients with metabolic dysfunction or chronic liver disease, perioperative dysbiosis may act as a “second hit”, superimposed on pre-existing ecological vulnerability and increased intestinal permea-

bility [21, 22]. Enhanced Recovery After Surgery (ERAS) pathways may mitigate-though not completely prevent-these perturbations, and emerging evidence suggests that this benefit may be partially mediated by preserving microbiota activity and maintaining intestinal barrier integrity [23-25].

The fragility of microbiota homeostasis is often evident before surgical incision. Traditional and contemporary approaches to bowel preparation and antibiotic prophylaxis have primarily focused on lowering luminal bacterial load to prevent infection, with limited consideration of long-term ecological consequences [26-28]. Recent sequencing studies have shown that mechanical bowel preparation and oral antibiotics can induce rapid, and sometimes profound, taxonomic changes in luminal microbial communities; however, these changes are heterogeneous and might not fully reflect alterations in mucosa-associated microbiota [29-31].

Preoperative dietary patterns also play a critical role. Diets characterized by Western-style patterns - high in fat and low in fiber - predispose patients to a less diverse and more pro-inflammatory microbiome, which experimental models have associated to impaired anastomotic healing and increased leakage rates [32-34]. Accumulating evidence from large multicenter cohorts in gastrointestinal cancer surgery has identified certain preoperative microbiota signature phenotypes, in combination with fecal biomarkers of intestinal environment, as predictors of postoperative infectious complications, indicating that pre-existing dysbiosis is more than a supporting feature of infirmity but rather a pathophysiological factor [35, 36]. Together, these observations indicate that many patients enter surgery with an already fragile microbial ecosystem that is highly susceptible to additional intraoperative and postoperative insults, including anesthetic exposure [37, 38].

Disruptions in microbiota homeostasis in the perioperative period can translate into clinically significant sequelae across the organ systems. The most convincing evidence arises from gastrointestinal surgery, where both prospective cohort and mechanistic studies have identified specific alterations in rectal and colonic microbiota associated with postoperative ileus, surgical site infection, and anastomotic leakage, characterized by depletion of beneficial commensals and enrichment of collagenase-producing or biofilm-forming organisms [39-41]. Similar patterns of reduced microbial diversity and enrichment of pro-inflammatory taxa have been associated with increased rates of infection, systemic inflammation, and impaired immune surveillance upon gastrectomy and other major abdominal procedures [42, 43]. In addition to local complications, perioperative microbiota disruption has also been implicated in postoperative neurocognitive disorders through the gut-brain axis, whereby microbially derived metabolites interact with microglial activation and neuroinflammation, especially in elderly and neurosurgical populations [44-46]. Collectively, these findings support a model in which microbiota destabilization amplifies surgical injury through a variety of mechanisms, including barrier dysfunction, inflammasome activation, and dysregulated host responses, contributing to a spectrum of surgically associated complications that extend beyond the gastrointestinal system [47].

From a systems perspective, this fragility has important implications for anesthetic practice and perioperative trial design. Given that anesthetic agents, opioids, and adjuncts are administered in the context of already dynamic and unstable microbiota, baseline microbial status should be considered in perioperative study design and individualized management. The vulnerability of perioperative gut microbiota homeostasis suggests that microbiome profiling may serve not only as a risk stratification tool but also as a potential biomarker for microbiota-sparing perioperative strategies, including choice of anesthetic regimen, opioid-sparing analgesia, targeted use of antibiotics, and microbiota-directed interventions. In the following sections, we build on this conceptual framework to examine how specific anesthetic agents and techniques interact with a vulnerable gut ecosystem, and how integration of microbiota-related metrics into anesthetic decision-making may facilitate a more precise and biologically informed approach to perioperative care (**Figure 1**).

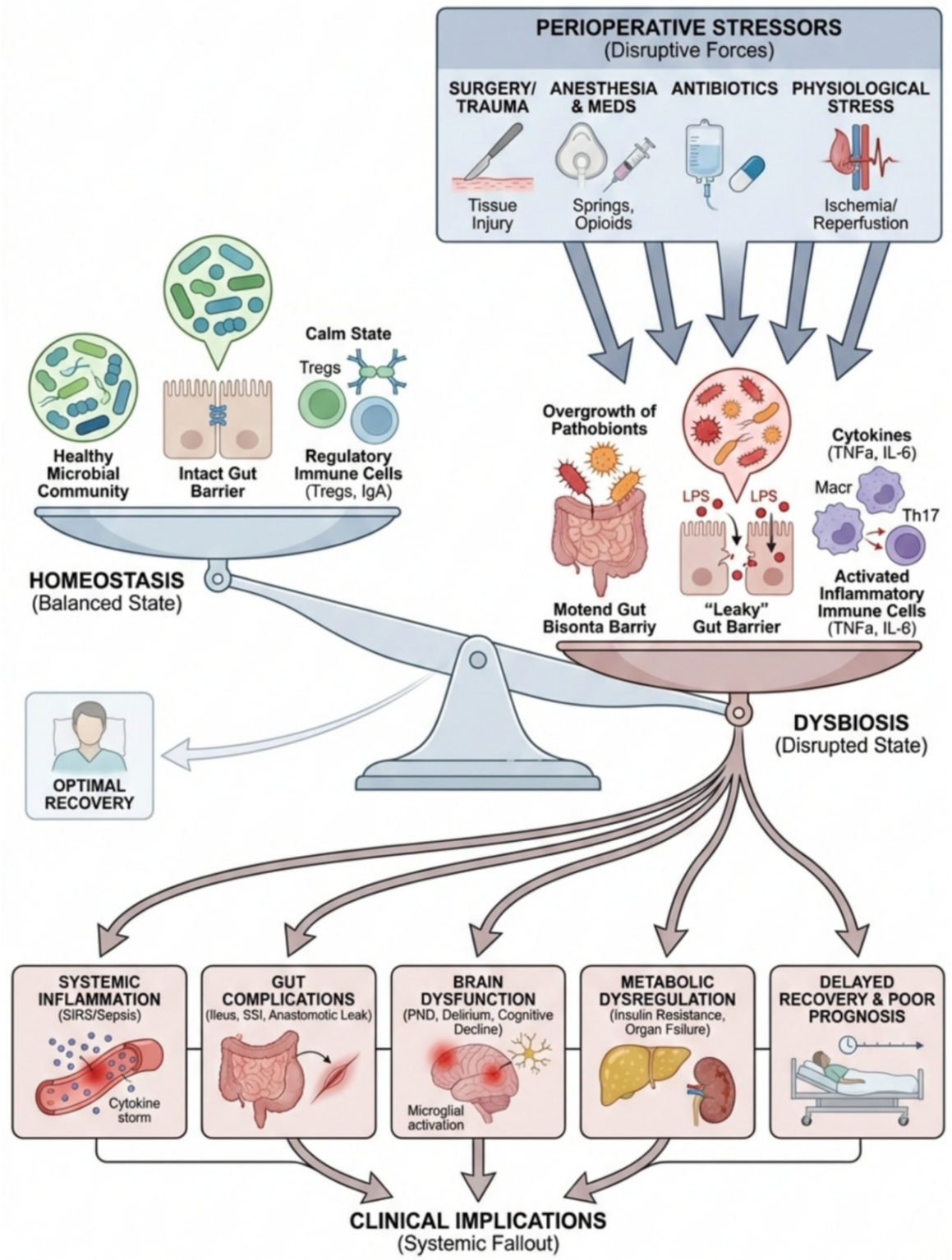

Figure 1. Fragility of perioperative gut microbiota homeostasis and its clinical implications. Perioperative stressors - including surgical trauma, anesthetic and analgesic medications, antibiotic exposure, and physiological stressors such as ischemia-reperfusion-act as disruptive forces on the intestinal ecosystem. In a homeostatic state (left), a diverse, balanced microbial community coexists with an intact mucus and epithelial barrier, abundant regulatory immune cell populations (e.g., Tregs), and predominantly anti-inflammatory signaling, collectively supporting optimal postoperative recovery. When the cumulative burden of perioperative stress exceeds the resilience of the

microbiota and intestinal barrier (right), pathobionts expansion occurs, accompanied by accumulation of LPS and other microbial products, disruption of tight junctions, and activation of pro-inflammatory cytokines (e.g., Th17 cells, TNF-α, IL-6), ultimately driving a shift toward dysbiosis. The central balance scale illustrates how relatively modest perturbations can shift the system from homeostasis to a disrupted state. Once dysbiosis is established, downstream systemic consequences emerge, including systemic inflammation, gastrointestinal complications, neurocognitive dysfunction (including perioperative neurocognitive disorders and delirium), metabolic dysregulation, and delayed recovery with poor prognosis. The figure highlights the inherent fragility of perioperative gut microbiota homeostasis and underscores the importance of maintaining this balance to improve clinical outcomes. Notes: SIRS: Systemic Inflammatory Response Syndrome; SSI: Surgical Site Infection; PND: Perioperative Neurocognitive Disorders; LPS: Lipopolysaccharide; Tregs: Regulatory T cells; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6; IL-10: Interleukin-10.

Mechanistic deepening: the bidirectional chemical dialogue between anesthetic agents and the microbiota

The relationship between anesthetic drugs and the gut microbiota is a bi-directional chemical communication, rather than a unidirectional neurotoxic effect on a passive ecosystem (**Figure 2**). On the one hand, anesthetics and perioperative co-medications alter the intestinal milieu by modulating perfusion, motility, mucus characteristics, epithelial permeability, and immune tone, thereby reshaping ecological niches in which microbial communities compete and coexist [48]. On the other hand, microbial communities react by altering their taxonomic makeup and metabolite production, including short-chain fatty acids, bile acid derivatives, tryptophan and phenolic metabolites, lipopolysaccharides, peptidoglycans, and other microbe-associated molecular patterns, which, in turn, induce host immune, vascular, and neural pathways, ultimately affecting anesthetic sensitivity, recovery trajectories, and susceptibility to complications [49, 50]. Emerging evidence suggests that the relationship is not a simplistic "anesthetic X induces dysbiosis Y", but rather, unique pharmacologic classes produce context-dependent microbial and metabolic signatures, shaped by baseline microbiota composition and host resilience.

From the "top-down" perspective, anesthetic exposure perturbs host determinants of microbial ecology. Volatile anesthetics and intravenous agents (e.g., propofol) can suppress gut motility, alter splanchnic perfusion, and transiently disrupt tight junctions, thereby modifying luminal transit time, oxygen gradients, and nutrient availability-key factors that govern microbial selection. In addition, many agents modulate epithelial and lamina propria immune responses, attenuating certain inflammatory cascades while impairing microbial clearance and phagocytic function, thus weakening host constrains on opportunistic pathobionts. Opioid analgesics further exacerbate these effects by inducing constipation, increasing intraluminal stasis, and activating μ-opioid receptors on enteric neurons and immune cells, thereby promoting the expansion of bile-tolerant organisms and the production of pro-inflammatory metabolites [51, 52]. In contrast, regional and neuraxial anesthesia techniques may better preserve gut perfusion and motility, illustrating how anesthetic strategies can indirectly yet significantly influence microbial composition and function [53, 54]. Across these pathways, the microbiota does not merely undergo passive injury but actively re-equilibrates in response to dynamic host environmental changes.

Equally important is the "bottom-up" dimension, whereby the microbiota regulates the pharmacokinetics and pharmacodynamics of anesthetic and analgesic agents. Microbial enzymes can directly biotransform drugs, including opioids, sedatives and adjuvant agents, into active or inactive metabolites, thereby altering systemic drug exposure and target engagement. In addition, microbiota-driven regulation of bile acid pools, short-chain fatty acid (SCFA) generation, and tryptophan metabolism can influence hepatic cytochrome activity, blood-brain barrier integrity, and glial cell activation, ultimately affecting anesthetic potency, emergence profiles, and susceptibility to neuroinflammation. Furthermore, microbiota-derived ligands for pattern recognition receptor (PRR), including TLRs and NLRs, exert tonic effects on systemic immune homeostasis. Perioperative alterations in these signaling pathways may skew host response toward hyperinflammation or immunosuppression in response to surgical stress and anesthesia exposure [55,

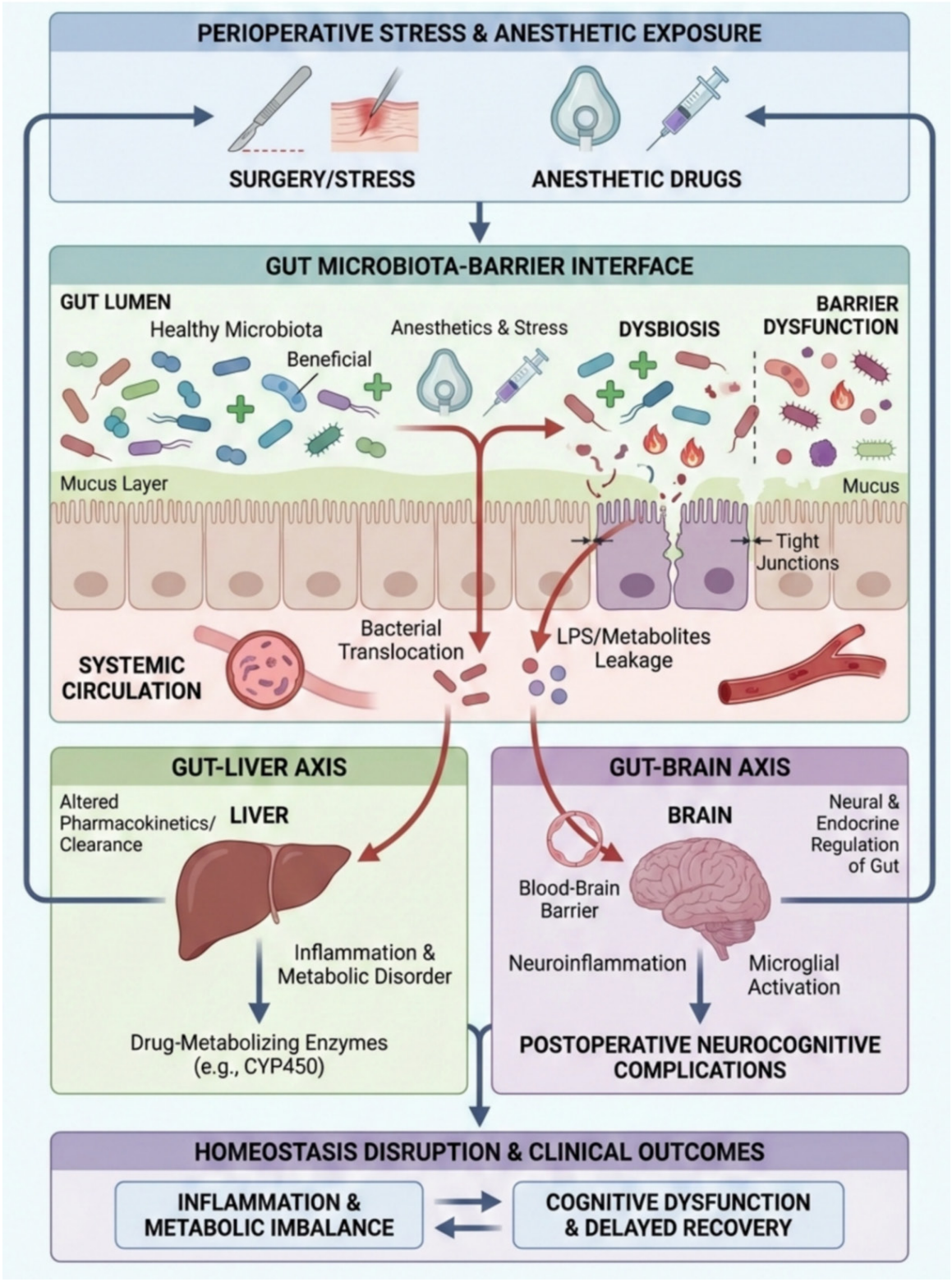

Figure 2. Mechanistic schema of the bidirectional interactions between perioperative gut microbiota homeostasis and anesthetic agents. Perioperative stressors (e.g., surgery, trauma, fasting) together with exposure to anesthetic and analgesic drugs, act on the gut lumen to shift a healthy, diverse microbiota toward dysbiosis, accompanied by impairment of the mucus layer and disruption of epithelial tight junctions. This disruption of gut microbiota-barrier homeostasis facilitates bacterial translocation and the systemic dissemination of LPS and other microbially derived

metabolites. Through the gut-liver axis, these signals drive hepatic inflammation and metabolic disturbance, modulate drug-metabolizing enzymes (e.g., CYP450), and thereby alter the pharmacokinetics and clearance of anesthetic agents. In parallel, via the gut-brain axis, circulating microbial products and inflammatory mediators compromise blood-brain barrier integrity, promote microglial activation and neuroinflammation, and modify neural regulation of gastrointestinal function, ultimately contributing to postoperative neurocognitive complications. Together, these intertwined pathways demonstrate that anesthetic agents not only disrupt gut microecological homeostasis but are also modulated by microbiota-dependent host responses, leading to systemic inflammation, metabolic imbalance, cognitive dysfunction, and delayed recovery. Notes: LPS: Lipopolysaccharide; CYP450: Cytochrome P450.

56]. Evidence from experimental models, including antibiotic depletion, germ-free models, and fecal microbiota transplantation, consistently demonstrates that manipulation of the gut microbiota can alter anesthetic requirements, pain behaviors, and cognitive outcomes, supporting a causal role for microbiota-driven bottom-up mechanisms [57].

From this mechanistic perspective, anesthetic-microbiota crosstalk can be viewed as a dynamic network of chemical interactions that is highly sensitive to preoperative microbiota composition, surgical context, and co-administered drugs. Distinct anesthetic and analgesic regimens appear to generate a distinct specific microbial and metabolic "fingerprint", which may partly explain interindividual variability in recovery trajectories and complication risk, even among patients receiving similar anesthetic techniques. However, current evidence remains fragmentary: most studies focus on isolated pathways, lack longitudinal sampling, and rarely integrate microbiome, metabolome, and immunophenotyping data within the same cohort. Mechanistically informed, multi-omics approaches in well-controlled clinical and experimental settings will be essential to move beyond associative findings, delineate causal pathways, and identify actionable targets (e.g., microbial taxa, metabolic products, or host receptors) for the development of microbiota-sparing or microbiota-modulating anesthetic strategies.

Distinct fingerprint signatures of anesthetic and analgesic agents

In addition to the generic concept of anesthesia-induced dysbiosis, growing evidence suggests that different anesthetic and analgesic agents may induce distinguishable microbiota-metabolite patterns rather than a uniform perturbation. These changes have been characterized not only at the taxonomic level but also across key metabolic and inflammatory pathways. Multi-omics studies have shown that perioperative courses that appear clinically comparable - such as those involving volatile anesthesia versus total intravenous anesthesia - may be associated with divergent microbial and metabolic responses over time, supporting the hypothesis that anesthetic agent selection is a major determinant of microbiome dynamics in response to surgical stress [58-61]. Notably, these signatures seem to complement, rather than replace, traditional host risk factors, including age, comorbidity burden, and underlying liver disease, underscoring the patient-specific and context-dependent nature of anesthetic-microbiota interactions [62, 63].

A representative example is volatile anesthetics and propofol. Clinical cohort studies in patients undergoing procedures such as nephrectomy have demonstrated that sevoflurane-, propofol-, and sevoflurane-propofol anesthesia are associated with distinct microbiota and metabolic profiles, despite similar surgical contexts. Patients receiving volatile anesthesia tend to exhibit greater reductions in microbial diversity and a shift toward pro-inflammatory metabolite signatures, whereas propofol-based or combined regimens are associated with less pronounced or qualitatively different alterations, including relative preservation of some SCFA producing taxa [64, 65]. Further studies of sevoflurane exposure in aged and juvenile rodent models also support these findings: sevoflurane exposure was associated with reproducible dysbiotic patterns characterized by depletion of beneficial commensals, enrichment of potentially pathogenic organisms, and alterations in amino acid and lipid metabolism. These changes have been associated with the NLRP3 inflammasome activation, microglial activation, and postoperative cognitive dysfunction [66, 67]. Although current evidence does not yet support definitive categorical assertions regarding the microbiota-safety and microbiota-toxicity of volatile and intravenous anesthetics, they do support the hypoth-

esis that volatile and intravenous anesthetics differ in the intensity and the direction of their microbiome imprint and the resulting neuroimmune downstream effects.

Analgesic strategies provide a parallel illustration of this agent-specific heterogeneity. Among systemic opioids, morphine has been the most intensively studied and consistently associated with a characteristic dysbiotic signature, including reduced microbial diversity, expansion of Gram-negative pathobionts, increased intestinal permeability, and disruption of bile acid and cholesterol metabolism along the gut-liver axis [68, 69]. These changes correlate with heightened mucosal and hepatic inflammation and may contribute to the development of opioid tolerance and exaggerated systemic inflammatory responses. Other opioids, such as fentanyl, may induce related but distinct microbiota perturbations, suggesting drug-specific differences in the degree and pattern of epithelial barrier disruption and antimicrobial peptide regulation [70-72]. In contrast, regional anesthesia techniques and multimodal opioid-sparing regimens, although less well characterized at the microbiome level, have been associated with more favorable immune profiles and reduced systemic inflammation, raising the possibility that such approaches may also be associated with a less disruptive microbial fingerprint; however, this hypothesis requires validation through well-designed longitudinal microbiome and metabolome studies [73, 74].

Collectively, current evidence suggest that perioperative anesthetic exposure should be viewed as a set of agent- and strategy-dependent microbiota effects occurring on a heterogeneous baseline ecological background. However, existing evidence base remains limited by small sample sizes, short follow-up durations, and substantial methodological heterogeneity in sequencing systems, bioinformatic pipelines, and control of perioperative covariates. Key priority for future research is to move beyond isolated single-agent comparisons toward integrative, multi-omics studies that can identify reproducible microbiota-metabolite clusters associated with specific anesthetic-analgesic regimens and clinical outcomes. Such efforts may eventually enable classification of anesthetic regimens based on their microbiota fingerprint and associated risk phenotypes. This framework could inform personalized anesthetic selection, facilitate the design of microbiota-sparing perioperative protocols, and help identify high-risk patients who may benefit from adjunctive microbiota implantation (**Figure 3**).

Perioperative microbiota-targeted precision intervention strategies

Recognition of the clinical relevance and high prevalence of perioperative dysbiosis has driven a transformation toward microbiota-oriented interventional strategies. These strategies can be conceptualized along two dimensions: the timing of intervention (prehabilitation, intraoperative protection, or postoperative restoration) and the degree of personalization (one-size-fits-all or microbiome-informed precision strategies). Traditional blanket-like interventions (e.g., empiric probiotic formulations) are slowly being replaced by more sophisticated frameworks that aim to tailor interventions based on individual risk profiles, underlying disease states (e.g. chronic liver disease along the gut-liver-anesthesia axis), and the expected individual microbiota effect of specific anesthetic and perioperative management strategies. This shifting paradigm positions the gut microbiota not only as a biomarker for risk stratification and therapeutic monitoring but also as a direct therapeutic target [75].

Among existing modalities, perioperative synbiotics and probiotics are the most extensively studied. Several randomized controlled trials and recent meta-analyses in colorectal, hepatopancreatobiliary, and upper gastrointestinal surgery indicate that appropriately selected formulations, timing, and dosing, particularly when administered during the pre-and early post-operative periods, can reduce the incidence of infectious complications, shorten hospital length of stay, and mitigate biochemical markers of systemic inflammation and intestinal permeability [76, 77]. These advantages appear most pronounced in composite endpoints of postoperative infection. Emerging evidence also suggests that perioperative pro-/synbiotics may help preserve microbial diversity and promote the abundance of SCFA-producing taxa, thereby functioning as ecological and clinical modulators [78]. However, variability in efficacy across studies indicates that off-the-shelf formulations should not be

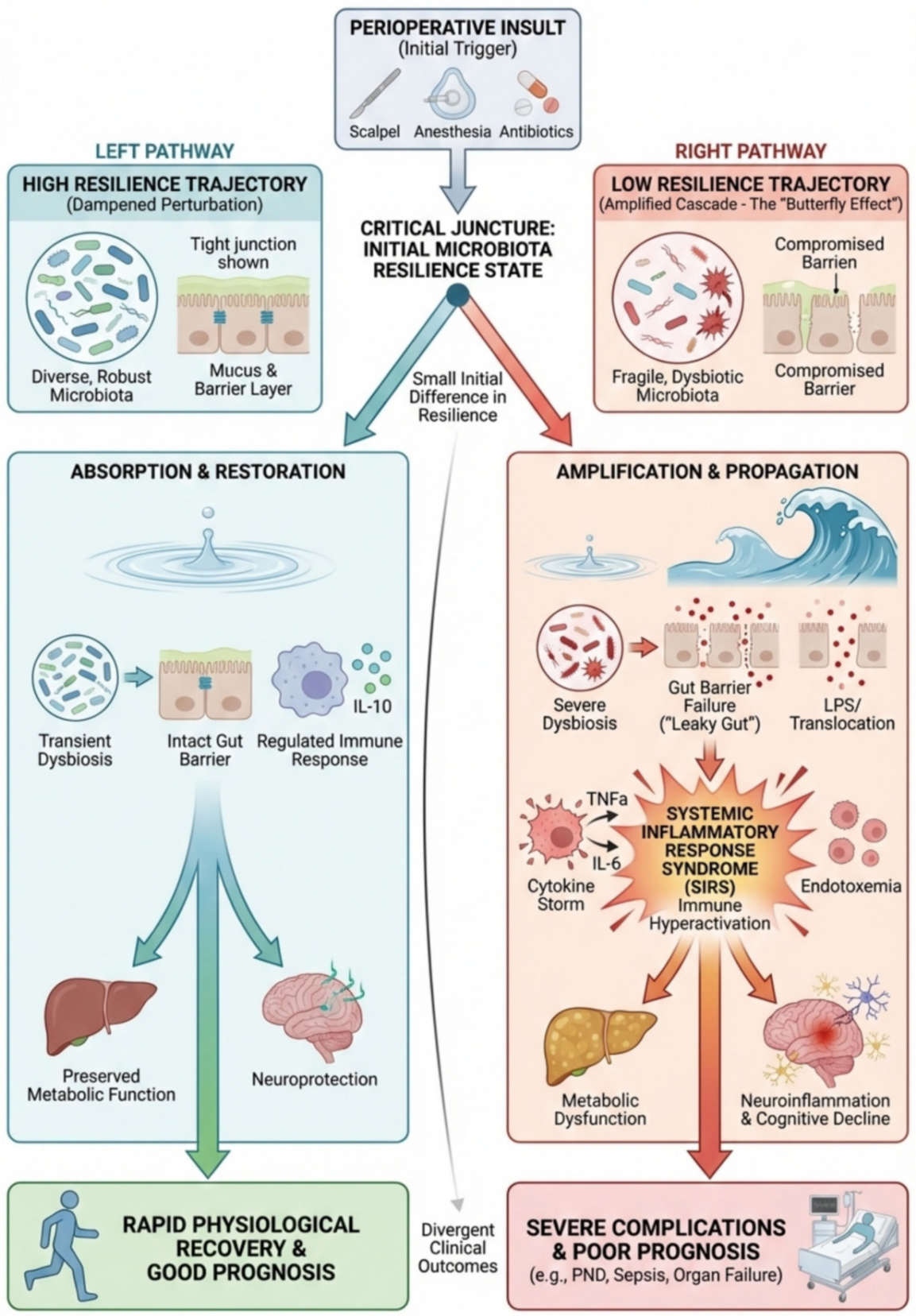

Figure 3. The "butterfly effect" of perioperative gut microbiota resilience on clinical trajectories. Perioperative insults - including surgical trauma, anesthesia, and antibiotics-act as initial triggers on a pre-existing state of microbiota

resilience. At a critical tipping point, even small differences in baseline resilience may divert patients into two divergent trajectories. On the left, the high-resilience pathway is characterized by a diverse, robust microbiota and an intact mucus layer, and preserved tight-junction barrier. Perioperative stress induces only transient dysbiosis, which is rapidly absorbed and restored through preservation of barrier integrity, anti-inflammatory mediators (e.g., IL-10), and a regulated immune response. Metabolic function in the liver is maintained, neuroinflammation is limited, and the host experiences rapid physiological recovery with a favorable prognosis. On the right, a low-resilience pathway begins with a fragile, dysbiotic microbiota and a compromised barrier. The same perioperative insult triggers an amplified cascade, including severe dysbiosis, gut barrier breakdown with lipopolysaccharide and bacterial translocation, and development of systemic inflammatory response syndrome with cytokine storm and endotoxemia. These processes drive metabolic dysfunction, neuroinflammation, and cognitive decline, culminating in severe complications and poor outcomes such as perioperative neurocognitive disorders, sepsis, and organ failure. The figure illustrates how modest initial differences in microbiota resilience can be magnified into dramatically different perioperative courses - the microbiome-mediated “butterfly effect”.

considered universal, and the future studies should incorporate baseline microbiome characterization to identify responsive patient subgroups and optimize intervention strategies.

Beyond probiotics and synbiotics, more intensive approaches such as fecal microbiota transplantation (FMT) and rationally designed microbial consortia offer the potential to reshape the gut microbiota at a systems level. Early studies suggest that carefully screened donor-derived FMT can transfer complex microbial communities and metabolite repertoires, with potential to restore microbial diversity, reestablish colonization resistance, and normalize bile acid and SCFA profiles more effectively than single-strain interventions. However, the implementation of FMT in the perioperative setting faces substantial challenges, including optimal timing relative to bowel preparation and antibiotic exposure, infectious risk, regulatory considerations, and acceptance by patients and clinicians. In parallel, postbiotic strategies that deliver defined microbial metabolites or structural components (e.g., specific SCFAs, bile acid derivatives, or bacterial cell wall fractions) aim to harness downstream effector pathways without requiring live microorganisms, potentially improving safety, reproducibility, and regulatory feasibility [79, 80]. These emerging modalities are particularly attractive in high-risk cohorts (such as patients with advanced liver disease or severe comorbidity), in whom targeted modulation of the gut-liver-anesthesia axis may significantly influence perioperative trajectories.

A truly precision-based approach, however, requires integration beyond microbiota-directed products alone. First, patients at high risk of dysbiosis-related complication (such as anastomotic leak, sepsis, acute kidney injury, and perioperative neurocognitive disorders) should be identified using microbiota-informed risk stratification models incorporating baseline microbial composition, metagenomic phenotypes, and metabolite profiles [81, 82]. Second, anesthetic and analgesic regimens should be optimized with consideration of microbiota preservation. This may include the use of opioid-sparing multimodal analgesia, avoidance of unnecessary antibiotic exposure, and selection of anesthetic techniques or drug combinations associated with less disruptive microbiota signatures in specific clinical contexts [83, 84]. Third, perioperative nutrition should be explicitly recognized as a key microbiota-directed intervention. Strategies such as early enteral nutrition, diets rich in fiber and polyphenol where feasible, and avoidance of prolonged parenteral nutrition without microbiota-supportive measures may play roles comparable in importance to pharmacologic measures [85, 86].

Finally, moving microbiota-targeted perioperative care from concept into routine practice will require a new generation of trials and analytic frameworks. Most existing randomized studies are underpowered for hard clinical endpoints, limited in follow-up duration, and rarely incorporate longitudinal, multi-omics profiling that links taxonomic changes to metabolite dynamics, immune phenotypes, and patient-centered outcomes. Future trials should aim to: (I) Stratify or enrich patient populations based on baseline microbiome features; (II) Compare clearly defined, microbiota-informed perioperative pathways (e.g., “microbiota-sparing anesthesia plus synbiotics” versus standard care); and (III) Integrate systems-level analyses to identify causal mediators and predictive biomarkers. Advances in rapid sequencing technologies, point-of-care metabolomics, and

machine learning-based risk modeling will be essential to operationalize these precision strategies within real-world perioperative workflows. As these tools mature, microbiota-targeted interventions are likely to evolve from adjunctive, empirical therapies to integral components of individualized perioperative plans, co-implemented by surgeons, anesthesiologists, and microbiome scientists to preserve gut ecosystem integrity while optimizing surgical and anesthetic outcomes.

Conclusions and future perspectives

Accumulating evidence has moved the gut microbiota from the periphery to the central position in the landscape of perioperative physiology. Surgical and anesthetic interventions occur against the background of a pre-existing microbial ecosystem shaped by age, comorbidities, diet, medications, and chronic inflammation. Within this framework, the perioperative period can be viewed as an ecological stress test, capable of driving a relatively compensated microbiota toward dysbiosis, characterized by loss of diversity, barrier destabilization, and maladaptive immune responses. These alterations have been increasingly correlated with a wide range of postoperative complications, including ileus, anastomotic failure, infections, and organ dysfunction, as well as perioperative neurocognitive disorders. Concurrently, growing mechanistic and clinical evidence suggests that anesthetic and analgesic drugs do not act unidirectionally upon this ecosystem but instead engage in a bidirectional chemical conversation this interaction influences drug disposition and immune homeostasis as well as neuroinflammatory activity. Collectively, these findings support a paradigm in which perioperative gut microbiota homeostasis functions both as a determinant and a mediator of anesthetic risk, thereby representing a rational target for precision perioperative medicine.

A key conceptual advance in recent research is the recognition that anesthetic and analgesic agents induce distinct microbiota-metabolite "fingerprints", rather than a uniform dysbiosis state. Intravenous anesthetics, opioid-sparing strategies, and volatile agents, seem to exert differential effects on microbial composition, metabolic activity, and host immune-neural interactions. These agent-specific signatures may help explain why patients undergoing ostensibly similar surgical and anesthetic procedures exhibit substantial variability in postoperative recovery trajectories.

Nonetheless, the current evidence base remains limited. Most studies are small in scale, and lack long-term follow-up, with few incorporating comprehensive multi-omics profiling. It is therefore premature to classify specific anesthetic agents or techniques as "microbiota-safe" or "microbiota-toxic". Future research should move beyond broad comparative approaches to identify reproducible and clinically meaningful microbiome signatures associated with specific anesthetic-analgesic regimens, patient characteristics, and postsurgical outcomes. This will require rigorously designed longitudinal cohorts with standardized protocols, harmonized bioinformatic pipelines, and careful control of key confounders, including diet, antibiotic exposure, and surgical complexity.

At the interventional level, the field is transitioning from empirical, non-specific approaches toward microbiota-informed precision strategies. Probiotics, synbiotics, and novel postbiotic or microbial consortium-based therapies show promise in reducing complications and preserving microbial function; however, their impact remain inconsistent and are likely influenced by baseline microbiome conditions. More advanced concepts, like microbiota-based risk stratification, microbiome-informed anesthetic selection, and targeted modulation of the gut-liver-brain axes are conceptually compelling but remain largely exploratory. Achieving this vision will require convergence of several enabling developments, including fast and sensitive perioperative microbiome and metabolome profiling technologies, validated risk models incorporating microbial, clinical, and potentially genetic data, and pragmatic clinical trials incorporating microbiota-related endpoints into perioperative care pathways. Importantly, these advances must be accompanied by careful consideration of feasibility, scalability, and equity, to ensure that microbiome-informed advancements can be implemented across diverse healthcare systems and patient groups, not just limited to highly specialized facilities.

Looking forward, perioperative microbiome research is poised to evolve from an observational discipline into a platform for designing and testing biologically informed clinical strategies. Future research priorities include elucidating causal mechanisms, identifying actionable microbial and host targets along the gut-liver-brain axes, leveraging systems biology and machine learning approaches to define microbiota-based risk phenotypes, and integrating microbiome considerations into clinical guidelines for anesthetic selection, analgesic management, and antimicrobial stewardship.

Achieving these goals will require genuinely multidisciplinary collaboration among anesthesiologists, surgeons, microbiologists, immunologists, neurologists, bioinformaticians, and clinical trialists. If successful, this effort has the potential to transform perioperative care - from a narrow focus on hemodynamics and pharmacology toward a broader, ecosystem-oriented approach that prioritizes the preservation of gut microbial homeostasis as a cornerstone of safe anesthesia and optimal surgical recovery.

Disclosure of conflict of interest

None.

Address correspondence to: Jiaru Yu, Department of Anesthesiology, The Second Affiliated Hospital of Jiaxing University, No. 1518 Huancheng North Road, Jiaxing 314000, Zhejiang, China. Tel: +86-18045464356; E-mail: yujiaru1120@163.com

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