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Review Article

Role of Gut Microbiota and Oxidative Stress in the Progression of Transplant-Related Complications following Hematopoietic Stem Cell Transplantation

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Hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, has curative potential for various hematologic malignancies but is associated with risks such as graft-versus-host disease (GvHD), severe bloodstream infection, viral pneumonia, idiopathic pneumonia syndrome (IPS), lung fibrosis, and sinusoidal obstruction syndrome (SOS), which severely deteriorate clinical outcomes and limit the wide application of HSCT. Recent research has provided important insights into the effects of gut microbiota and oxidative stress (OS) on HSCT complications. Therefore, based on recent studies, we describe intestinal dysbiosis and OS in patients with HSCT and review recent molecular findings underlying the causal relationships of gut microbiota, OS, and transplant-related complications, focusing particularly on the involvement of gut microbiota-mediated OS in postengraftment complications. Also, we discuss the use of antioxidative and anti-inflammatory probiotics to manipulate gut microbiota and OS, which have been associated with promising effects in improving HSCT outcomes.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially life-saving procedure for a multitude of congenital and acquired diseases of the hematopoietic system, including malignancy, severe hematopoietic deficiency, and immune dysfunction [1]. Human hematopoietic stem cells (HSCs) with strong regenerative potential are uniquely implanted into the bone marrow of recipients, providing long-term multilineage hematopoiesis and reconstituting a complete hematopoietic system [2]. Complications after HSCT, including graft-versus-host disease (GvHD), severe

bloodstream infection, viral pneumonia, idiopathic pneumonia syndrome (IPS), and sinusoidal obstruction syndrome (SOS) are closely associated with peritransplant morbidity and mortality and severely limit the wide application of HSCT. Despite efforts made in improving transplant outcomes, such as the high resolution of human histocompatibility locus genotyping, prophylactic use of calcineurin inhibitors [3], and infection control using wide-spectrum antibiotics [4], the management of postengraftment complications remains the cornerstone of successful HSCT.

The gut microbiota benefits from the warm nutrient-rich environment of a healthy gut and serves as an important health regulator for hosts. Firmicutes including *Lactobacillus*, *Streptococcus*, *Mycoplasma*, *Clostridium*, and Bacteroidetes comprise 90% of the total gut microbiota. Healthy gut microbiota contributes to intestinal ecosystem homeostasis. Rapid shifts in the composition and function of intestinal microbial communities, known as intestinal dysbiosis, are associated with intestinal barrier disruption and lead to the development of inflammatory [5], cancer [6], metabolic diseases [7], and neurodegenerative diseases [8]. Patients undergoing HSCT display significant changes in the gut microbiota due to the underlying malignancy and exposures to extensive chemotherapy, immunosuppressants, and systemic antibiotics [9]. Due to the clinical significance of gut microbiota, significant interest has emerged to understand the interplay between gut microbiota and HSCT-related complications and reveal the therapeutic value of this interaction.

Reactive oxygen species (ROS) including hydroxyl radicals (OH), superoxide anions, and hydrogen peroxide (H_2O_2) are byproducts of oxidative phosphorylation and trigger the activation of cyclooxygenases, nitric oxide (NO) synthase, lipoxygenases, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. HSCTs are known to increase the intracellular and extracellular accumulation of ROS, leading to an oxidative stress (OS) status for the occurrence of chemoradiotherapy conditioning and iron overload. Moreover, many recent studies have shown that both commensal and pathogenic bacteria can alter ROS production and promote the progression of neurodegeneration [10], fatty liver disease [11], and diabetes mellitus [12] (Table 1). OS impairs hematopoietic progenitor function and is potentially associated with posttransplant complications, leading to adverse clinical outcomes.

Targeting the OS and gut microbiota may represent an attractive therapeutic avenue for the management of transplant-related complications after HSCT. This review provides an in-depth examination of the crosstalk between OS, the gut microbiota, and transplant-related complications after HSCT. We first briefly reviewed the intestinal dysbiosis and OS in patients who underwent HSCT followed by comprehensive scrutiny of recent molecular findings underlying the causal relationships between gut microbiota, OS, and transplant-related complications, focusing on the gut microbiota-mediated OS involved in postengraftment complications. A better understanding of these relationships in patients with HSCT may allow unraveling the treatment for transplant-related complications by targeting OS and gut microbiota.

2. Intestinal Dysbiosis in Patients Undergoing HSCT: Adverse Effect of Conditioning Regimen and Prophylactic Antibiotics

Gut microbiota can promote intestinal homeostasis and protect intestinal integrity by supporting mucosal immunity maturation and preventing (invading) pathogen colonization [13]. Multiple factors can influence the compositional and functional dynamic balance of the intestinal microbiota, resulting in dysbiosis. HSCT recipients are particularly vulnerable to dysbiosis because of their underlying malignancies, long-term hospitalizations, prolonged application of antibiotics, and the use of preparative regimens prior to transplantation [14].

Dysbiosis in HSCT patients commonly manifests as a reduction in gut microbial diversity, diminished strictly anaerobic commensal bacteria, and expansion of pathogenic bacteria. Metagenomic analysis revealed the mean urinary indoxyl sulfate levels that can serve as an indirect marker of bacterial diversity in all patients receiving allo-HSCT dropped from 42.5 ± 11 mmol/L to 11.8 ± 2.8 mmol/L [15]. Intensive chemotherapy and/or radiation preparative regimens are responsible for the expansion of *Lactobacillales* and *Enterobacteriales* and the prominent loss of *Clostridiales* in mice [16]. Patients routinely consume antimicrobials prophylactically to diminish anaerobic bacteria and prevent opportunistic infections in the early posttransplantation period. However, metagenomic analysis of the stool microbiome revealed that microbial composition shifts and diversity loss were more pronounced after extensive antimicrobial exposure in HSCT patients [15]. The drastic loss of diversity in the microbiota is often accompanied by the expansion of a single taxon. *Enterococcus* predominance is more obvious under exposure to antibiotics such as ciprofloxacin and metronidazole [17] with a notable expansion of *E. faecium* and a complementary decrease in Firmicutes and other commensal phyla [15]. Rifaximin is a prophylactic antibiotic that effectively reduces intestinal infections and subsequent acute GvHD [18]. However, new research shows that rifaximin could contribute to microbiome disruption and favor an outbreak of life-threatening *Candida* spp. infections [19]. Microbial SCFAs, including acetate, butyrate, and propionate, are products of carbohydrate fermentation by the anaerobic commensal bacteria (*Clostridia* spp., for instance). SCFAs can preserve intestinal barrier integrity by supporting the functions of intestinal epithelial and goblet cells through coordinated regulation of tight junction proteins. Furthermore, SCFAs can induce tolerance and inhibit inflammatory cascade mediated by inhibiting nuclear factor kappa b (NF-κB) activation in macrophages, inducing colonic regulatory T (Treg) cell expansion, and upregulating gut-homing molecules and forkhead box protein P3 (Foxp3) of Treg cells [20]. The post-HSCT abundance of butyrogenic bacteria (mainly *Clostridia*) in the intestinal microbiota is higher in patients with resistance to lower tract respiratory infections and lower in patients who are susceptible to acute GvHD (aGvHD) [21].

A low diversity of the intestinal microbiota from allo-HSCT recipients was associated with significantly increased mortality (52%) compared with a high diversity of the intestinal microbiota (8%). Microbiota disruption characterized

Table 1: Role of gut microbiota-derived oxidative stress in the progressions of different diseases.

Intestinal microbiota	Mechanisms	Relative diseases	Reference
Enterococci faecalis ↑	Increase the production of hydroxyl radicals, contribute to DNA breaks, point mutations, and protein-DNA crosslinking, and induce aneuploidy in colonic epithelial cells	Colorectal cancer	[110]
Proteobacteria ↑ *Bifidobacteria* ↓	Contributes to the occurrence of dementia not only through the significant reduction of beneficial SCFAs but also through interfering with lipid metabolism	Alzheimer's disease	[111]
Gut-lung axis	Activating oxidative stress through TLR4/NF-kB pathway in the lung and mediating lung injury through the regulation of the gut barrier	Acute lung injury	[112]
Butyrate producers ↓: *Fusobacterium* *Veillonella* *Atopobium parvulum*	Dysbiosis dampen host H_2S defense systems induce mitochondrial dysfunction likely resulting in ROS production, contributing to mucus degradation, opening the intestinal barrier to toxic compounds and pathobionts	Crohn's disease	[113]
Prevotella *Clostridium*	Produce endogenous H_2, which have antioxidant properties to neutralize toxic hydroxyl radicals, downregulate the expression of proinflammatory factors, and preserve cerebrovascular reactivity	Parkinson's disease	[114]
Escherichia coli ↑	Increase production of uric acid, which contributes to the overproduction of oxygen free radicals, vascular endothelial dysfunction, and inflammation	Atherosclerosis	[115]
Eggerthella lenta ↑ *Fusobacterium nucleatum* ↑	Increase serum uraemic toxins, which are relative to increased severity of oxidative stress, glomerulosclerosis, and renal fibrosis and increased serum levels of creatinine and/or urea in sham-fed rats	End-stage renal disease	[116]
H. pylori	Produce and induce the production of ROS by neutrophils and macrophages	—	[117]
Lactobacilli *Bifidobacteria*	High catalase and α,α-diphenyl-β-picrylhydrazyl free radical scavenging activity	Anticancer effect	[118]
Lactobacillus rhamnosus GG	Ameliorates alcohol-induced intestinal oxidative stress, intestinal hyperpermeability, and liver injury in rodent models of alcohol steatohepatitis	Alcoholic liver disease	[119]

by loss of diversity and single taxa domination is particularly associated with negative outcomes in allo-HSCT recipients. The domination of enterococci in posttransplant stool specimens is positively related to the subsequent development of gastrointestinal GvHD, and the mean proportion of enterococci increased by 53% at the time of active GvHD [15, 22]. Also, intestinal dysbiosis in HSCT patients is correlated with multiple infections including bloodstream infection [23], diarrhea [9], multidrug-resistant organism (MDRO) infection [24], and pulmonary infections [25]. Moreover, a retrospective observational analysis of 541 patients undergoing allo-HSCT identified that the intestinal microbiota could be associated with relapse/progression of disease after allo-HSCT [26].

3. Oxidative Stress in Patients Undergoing HSCT

3.1. ROS Generation in HSCT Patients: Conditioning Regimens and Iron Overload. Sustained and high-quality transplantation of donor HSCs requires pretransplantation adaptation. Chemotherapy and total-body irradiation are widely used as myeloablative conditioning regimens in patients before HSCT and remove most of the hematopoietic and immune systems of the host. Ionizing radiation can penetrate cells in living organisms and generate ROS via water radiolysis [27]. ROS react rapidly with macromolecules, including proteins, nucleic acids, and lipids, leading to cell damage and apoptotic cell death [28]. Damaged tissues release damage-associated molecular patterns (DAMPs) and initiate acute inflammatory responses through the activation of mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) signaling cascades. Such pathways are also regarded as the major mediators or inducers of the propagation of radiation-induced bystander effects that induce ROS to increase and replicate irradiation-related DNA damage in nonirradiated cells [29].

Cytostatic agents, including cyclophosphamide (CTX), busulfan, etoposide, melphalan, and carmustine (BCNU), are widely used in HSCT preconditioning to exert their antitumor action and reduce the recurrence rate. However, in recent years, the accumulation of free radicals has been implicated in the administration of cytostatic agents in various categories both *in vitro* and *in vivo*. Bone marrow stromal cells from patients receiving daunorubicin secreted higher levels of H_2O_2 than that of healthy control participants, leading to the accumulation of DNA damage in cocultured hematopoietic cells [30]. Chemotherapeutic agents

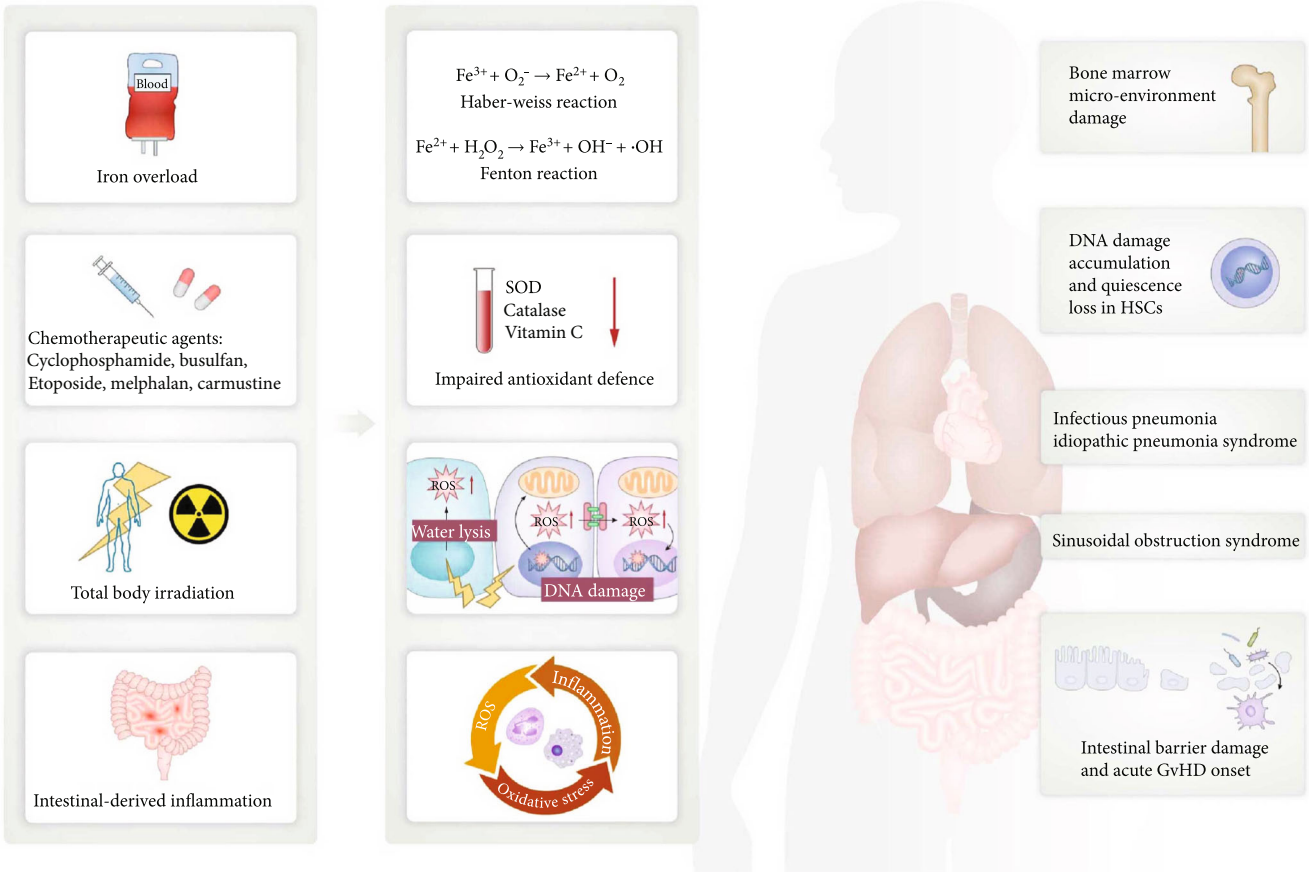

Figure 1: Mechanisms of oxidative stress during HSCT and its impact on the human body. Preengraftment conditioning with chemotherapy and total body irradiation are leading causes of disruption of redox balance and oxidative stress status in patients who underwent HSCT through increasing free radical production and diminishing host antioxidant defense. Iron overload increases ROS production via Haber-Weiss and Fenton reactions. Inflammatory cell infiltration during intestinal inflammation produces excessive oxidative intermediate ROS, which directly damages tissues and further promotes inflammatory response. Oxidative stress status in HSCT patients may contribute to subsequent transplant-related complications including bone marrow microenvironment damage, HSC dysfunction, intestinal barrier damage, and liver and lung injury. HSCT: hematopoietic stem cell transplantation; ROS: reactive oxygen species; HSCs: hematopoietic stem cells.

also disrupt redox balance by impairing antioxidant defense (e.g., superoxide dismutase and catalase) in human beings [31]. Plasma levels of vitamin C and catalase, which are powerful antioxidants for scavenging O^{2-}, H_2O_2, and OH^-, decline after the application of melphalan and CTX-BCNU-etoposide conditioning regimens [32]. The oxidant effects of CTX are associated with its active metabolites, such as phosphoramide mustard and acrolein, resulting in the accumulation of ROS, which can cause DNA damage and genetic instability, inducing bone marrow suppression [33]. Moreover, chemotherapy with busulfan, BCNU, and cisplatin can cause depletion of plasma glutathione, a nonenzymatic antioxidant [34], and thus amplify oxidative stress.

Iron is a critical cofactor for proteins in the respiratory chain and for cell growth and multiplication. It is potentially toxic to the host when excessive iron is deposited in the cells and tissues of some parenchymal organs. This condition is known as iron overload and is defined by elevated ferritin and liver iron content of approximately 30% and 32%–60%, respectively. Iron overload is a common event associated with HSCT due to the following possible reasons (Figure 1): (1) patients with hematologic diseases usually receive multiple red blood cell transfusions before and after HSCT; (2) chemotherapeutic agents inhibit erythropoiesis, resulting in iron underutilization; (3) the bone marrow, tumor cells, and liver are damaged after high-dose preconditioning, resulting in the release of internal iron pools. The most damaging effect of iron overload is the cycling between Fe^{2+} and Fe^{3+} via Haber-Weiss and Fenton reactions, ultimately generating reactive and toxic free radicals, such as OH^- and HO. Iron toxicity induces ROS and triggers inflammation, mediates oxidative and genotoxic stress of HSCs to damage the graft, and promotes recurrence, further damaging the already dysfunctional bone marrow microenvironment of HSCT recipients. Elevated ferritin levels have been associated with decreased overall survival, increased risk of infections, aGvHD, and sinusoidal occlusive disease [35].

3.2. Microbiome Changes May Affect ROS Levels in HSCT Patients. OS in HSCT patients induced by pretransplant conditioning and iron overload has been reported in the

literature; however, research on the association between microbiota-derived OS and transplant-related complications and outcomes is limited. The clinical significance of gut microbiota-derived OS in a multitude of diseases, including inflammatory, cancer, metabolic, and neurodegenerative diseases, indicates that changes in intestinal homeostasis can extensively influence the OS status in different systems of the body. Specific commensal and pathogenic bacteria can stimulate OS in the intestinal system. Commensal bacteria induce superoxide production by NADPH oxidase-1 and increase cellular ROS by stimulating formyl-peptide receptors on macrophages and neutrophils, resulting in inflammation of the intestinal epithelium [36]. Gut *Lactobacilli* and *Bifidobacterium* can convert nitrate and nitrites into NO, making the gut epithelia a rich source of NO. NO at high concentrations results in a detrimental effect due to the production of ROS, such as superoxide and H_2O_2, which further form highly reactive hydroxyl radicals [10]. *E. faecalis* produces substantial extracellular superoxide and derivative reactive nitrogen and oxygen species, such as H_2O_2 and OH, through the autoxidation of membrane-associated demethylmenaquinone [37]. However, OS occurring during intestinal instability and inflammation is a risk factor for dysbiosis because it strongly decreases microbial diversity and promotes the expansion of specific bacterial taxa. Leukocyte infiltration accompanied by the generation of reactive oxygen and nitrogen species during intestinal inflammation kills strictly anaerobic bacteria that are susceptible to oxygen intoxication and also promotes the selective growth of bacterial groups including *Enterobacteriaceae* (*Salmonella* and *Citrobacter*) as well as *Escherichia coli* through nitrate and tetrathionate respiration [38, 39].

3.3. The Adverse Effects of Excessive ROS and OS Status on HSCT Outcomes. OS is commonly resulting from chronic inflammation and subsequent generation of ROS and nitrogen species that are capable of damaging cellular DNA, protein, and organelles, thus altering gene expression and cell phenotypic traits. OS is suspected to promote cancer and contribute to diverse degenerative neurological disorders, cardiac dysfunction, and aging. The biological characteristics of HSCs are tightly regulated by the OS, and the control of ROS levels is important to maintain their self-renewal capacity. At low concentrations, ROS and reactive nitrogen species control diverse cellular functions, such as stem cell differentiation, and are used in intercellular communication. Murine HSCs with low ROS levels are more quiescent and exhibit increased longitudinal self-renewal and pluripotent differentiation compared to HSCs with higher ROS levels [40]. Exceedingly high ROS levels, which occur during important OS conditions such as chronic inflammation or iron overload, can promote quiescence loss and subsequently limit the capacity for regeneration and reconstitution of the entire hematopoietic system after transplantation into recipients [41, 42]. Excess free radicals and ROS cause severe damage to biological macromolecules (especially DNA damage) and dysregulation of the cell cycle, leading to inflammation and injury to the intestinal epithelium as well as intestinal dysbiosis, which heralds adverse outcomes and is associated with deteriorated overall survival after HSCT [43].

4. Gastrointestinal Toxicities and Bloodstream Infection after HSCT

Patients undergoing HSCT and routinely receiving immunosuppressive therapy are at a high risk of catastrophic bloodstream infections (BSIs); such infections are associated with significant morbidity and mortality after HSCT. In a case-cohort study of 16,875 pediatric and adult patients who underwent HSCT, 13% developed BSI due to bacterial translocation across the compromised mucosal barrier [44].

Mucosal barrier injury is also a frequent complication of allo-HSCT and an independent risk factor for the invasion of the gut microbiota into the bloodstream. Healthy intestinal epithelial cells, including intestinal stem cells, goblet cells, and Paneth cells, are connected by tight junctions and assemble into the intestinal epithelium. The intestinal epithelium, with a mucus layer, provides a physical and biochemical barrier, limiting the penetration of microbes and intestinal luminal contents into the host tissues. Pretransplant conditioning with radiation and chemotherapy is associated with increased ROS levels. Excessive OS causes DNA damage, inflammation, and cell apoptosis, leading to shifts in the microbiota, intestinal leakage, and radiation-induced enteritis. Chemoradiation therapy-induced DNA damage promotes the production of epithelial-derived interleukin-(IL-) 1β, which initiates intestinal barrier damage by compromising epithelial tight junctions [45]. Patients receiving pretransplant conditioning are not only susceptible to aggravated gastrointestinal epithelial cell damage but also to the elimination of circulating granulocytes and monocytes, markedly increasing susceptibility to subsequent bacterial translocations and disseminated infections [46, 47]. Iron overload is also related to OS status in HSCT patients and can cause tissue damage by protein oxidation, membrane lipid peroxidation, and nucleic acid modification, with the conversion of H_2O_2 to ROS [43]. Patients with high pretransplant serum ferritin, a surrogate indicator of tissue iron overload, have an increased incidence of BSI/death (60 vs. 44%, $P = 0.042$) than those with normal levels of pretransplant serum ferritin [35]. The severity of intestinal injury (also referred to as mucositis) after myeloablative conditioning is considered to be the most important determinant of the post-HSCT inflammatory response and is associated with the occurrence of inflammatory complications, including bacteremia, lung injury, and GvHD [48].

E. coli and *Klebsiella pneumoniae* BSIs with concomitant gut colonization by these organisms suggest that profound disturbances in the gut microbiota populations play an important role in BSI after HSCT [49]. Furthermore, the dominance of a single bacterial genus such as *Enterococcus* (vancomycin-resistant *Enterococcus* [23]), *Streptococcus* (viridian-group *Streptococcus* [50]), and various Proteobacteria [24] has been identified as the most common cause of bacteremia.

It is imperative to develop strategies to maintain the gut microbiota and gastrointestinal health to prevent subsequent enteric bacterial BSI and improve survival [51]. Prophylactic administration of fluoroquinolones, such as ciprofloxacin and levofloxacin, can reduce the risk of intestinal domination with Gram-negative microbes,

including *Proteobacteria* [52] (*Escherichia*, *Klebsiella*, and *Enterobacter*) [53], which are significantly associated with decreased bacteremia without increased risk of *Clostridium difficile*-associated diarrhea, aGVHD, or MDRO [54]. In addition to the prophylactic use of antimicrobial agents, gut decontamination with nonabsorbable antibiotics in the peri-HSCT period was reported to protect against gut-derived BSI by decreasing the microbial load of gut pathogens [55]. For intestinal barrier protection, the IL-1 receptor antagonist anakinra and anti-IL-1β antibody canakinumab limit the inflammatory reaction and improve intestinal barrier integrity in HSCT patients and murine [45, 56].

5. Graft-Versus-Host Disease after HSCT

5.1. Pathophysiology of Acute GvHD (aGvHD). GvHD is a common secondary disease in patients undergoing HSCT, which has long limited the efficacy of HSCT. Before transplantation, the patient's tissues and immune system have been profoundly damaged due to underlying disease, treatment for the disease, infections, and the conditioning regimen. Allogenic T cells from a foreign donor activate and respond upon binding human leukocyte antigens that are expressed on host tissue. A compromised host immune system is incapable of rejecting the immunocompetent cells, leading to amplified $CD4^+/CD8^+$ T cell activation and subsequent GvHD initiation. Subsequently, cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells induce the target cells' apoptosis through the Fas/Fas ligand pathway and perforin/granzyme pathway. Furthermore, inflammatory cytokines synergize with CTLs, resulting in further tissue injury and possible target organ dysfunction (Figure 2). Active GvHD primarily targets the skin (81%), gastrointestinal tract (54%), and liver (50%) of the hosts [57], closely associated with nonrelapse mortality following HSCT.

5.2. Intestinal Barrier, Microbial Dysbiosis, and the Onset of aGvHD. Damage to host tissues, especially the intestinal mucosa, caused by the conditioning regimen, is the most important initial step in the pathophysiology of aGvHD. Pretransplant conditioning regimens and GvHD can directly impair gut epithelium, especially Paneth cells. Paneth cell damage contributes to the loss of antimicrobial peptides (e.g., α-defensins) and growth factors (e.g., epidermal growth factor and transforming growth factor-α), then accelerates the loss of microbial diversity, and compromises epithelial regeneration capacity in GvHD, which leads to a higher risk of nonrelapse mortality [58]. Early studies reported that the GvHD-related mortality was significantly reduced in germ-free mice or when intestinal decontamination was performed [17, 59]. A longitudinal study reported that the development of GvHD was preceded by remarkable shifts in the gut microbiota that can serve as an early predictor of GvHD and transplant-related mortality after HSCT [60], with a predominant role played by Gram-positive bacteria belonging to Firmicutes phylum [61]. The hypothesis that lymphocytes sensitized against microbial antigens cross-react with epithelial antigens in GvHD is the most widely accepted model of microbial interactions in the pathogenesis of GvHD. Microbial products like lipopolysaccharide (LPS) and other pathogen-associated molecular patterns (PAMPs) systemically translocate from the bowel lumen through a damaged intestinal mucosa to the systemic circulation and then stimulate mononuclear cells (monocytes/macrophages) via pathogen recognition receptor (PRR) family such as NOD-like receptors (NLRs) and Toll-like receptors (TLRs) [62]. The amplified activation of these antigen-presenting cells triggers a cytokine storm (tumor necrosis factor-α (TNF-α) and IL-1) and a lower Treg/T helper (Th) 17 cell ratio, leading to amplification and propagation of a cytokine storm. These cytokines induce inflammatory damage and increase the expression of major histocompatibility complex (MHC) antigens and adhesion molecules in host tissues, enhancing the alloreactivity of mature donor T cells against host tissues, which are equivalent to GvHD [63, 64].

High-throughput metabolomic analysis revealed that GvHD development seems to be associated with major metabolomic changes in the intestinal microbiota compared with patients who did not develop GvHD. AhRs can modulate Th17 response and encourage tolerance by promoting Treg cells [65]. Microbially derived indole compounds are AhR ligands, which show a significant decrease, even undetectable in recipients with GvHD, and are associated with GvHD onset and severity. In addition, reduced plasmalogens, together with increased bile acids and polyunsaturated acids, are potential metabolomic pathways that could be involved in the early proinflammatory response during GvHD [66]. Mucosa-associated invariant T (MAIT) cells are a group of innate-like T cells that inhibit the proliferation of $CD4^+$ T cells. Poor reconstitution of MAIT cells after HSCT is significantly associated with the development and severity of GvHD [67]. Peripheral expansion of MAIT cells requires riboflavin (vitamin B2), the metabolite derived from healthy microbiota, which was observed to be significantly decreased in disrupted microbiota of HSCT patients [68]. Intestinal microbial metabolite plasmalogens produced by *Clostridium* strains and *Bifidobacterium longum* have many antioxidant effects in vitro and in vivo [69]. The level of microbiota-derived plasmalogens was dramatically low at the onset of aGvHD, leading to an imbalance between oxidation and antioxidation preceding GvHD. Increasing research on the crosstalk between the host and gut microbiota has provided opportunities to better understand the complex network of GvHD and optimize therapeutic strategies for decreasing HSCT-related morbidity and mortality.

5.3. GvHD Treatments Based on Targeting the Gut Microbiota. Prevention of GvHD mainly focuses on T cell depletion and regulation of T cell activation, proliferation, effector, and regulatory functions. Multimodal treatment is often used, but systemic corticosteroids are usually the mainstay of GvHD treatment. From the perspective of gut microbiota, restoring the intestinal epithelium and maintaining intestinal homeostasis represents the adjunct therapeutic strategies to standard immunosuppressive treatment of GvHD without compromising graft-versus-leukemia (GVL) effects. The GVL effect is a type of graft-versus-host

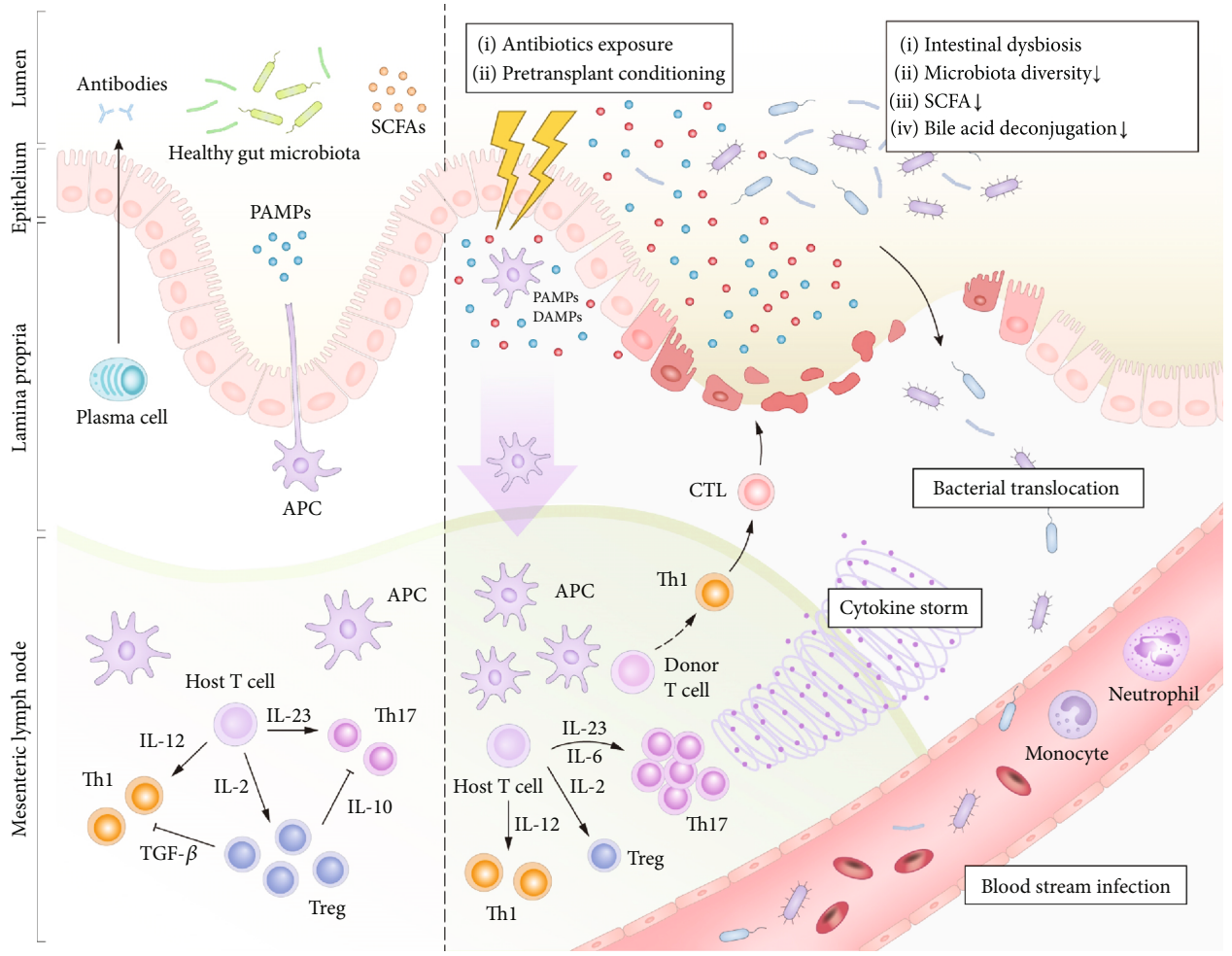

Figure 2: The intestinal damage and the pathogenesis of BSI and GvHD. A healthy intestinal system is important to maintain immune homeostasis. The intestinal homeostasis and epithelial cells are damaged by the cytotoxic conditioning regimen as well as by extensive antibiotic exposure, leading to disruption of the intestinal barrier, intestinal dysbiosis, and decreased production of beneficial metabolites (e.g., SCFAs). Bacteria translocate into circulation, leading to BSI and disseminated infections. DAMPs released by the dying intestinal epithelial cells as well as translocating bacteria and PAMPs activate host APCs resulting in a cytokine storm and donor T cell activation. T cells subsequently proliferate and differentiate into Th1 and Th17 types, which are involved in the activation of CTL that mediate tissue damage. Effector T cells together with cytokine storm attack the epithelial cells of the skin, liver, lung, and gastrointestinal tract, culminating in clinically GvHD. SCFA: short-chain fatty acid; BSI: bloodstream infection; DAMP: danger-associated molecular pattern; PAMP: pathogen-associated molecular pattern; APC: antigen-presenting cell; CTL: cytotoxic T lymphocytes; GVHD: graft-vs.-host disease.

reaction targeting leukemic cells in recipients, leading to reduced recurrence and superior survival [70]. Enteral nutrition as first-line nutritional support in patients who undergo HSCT can maintain the intestinal microecology and effectively inhibit GvHD onset [71]. Pretransplant administration of IL-25, a growth factor for goblet cells, allowed the conservation of goblet cells, prevented bacterial translocation, reduced plasma concentrations of interferon-γ (IFN-γ) and IL-6, and ameliorated GvHD [72]. The glucagon-like peptide 2 promotes the regeneration of Paneth cells and intestinal stem cells, which reduces aGvHD and steroid-refractory GvHD without compromising GVL effects in multiple mouse models [73]. A clinical trial (NCT02641236) revealed a decrease in the incidence of aGvHD in patients who underwent gut decontamination with oral vancomycin and polymyxin B; however, these investigations need to be significantly expanded [55]. Prophylactic administration of antimicrobials is a controversial topic because systemic antibiotic exposure not only suppresses anaerobic bacterial growth but also causes microbial diversity loss, decreases the production of anti-inflammatory SCFAs, and increases the incidence and severity of GvHD [74]. On the other hand, fecal microbiota transplantation (FMT) and probiotic supplementation have been analyzed in clinical trials, with a promising therapeutic value of restoring the intestinal microbiota, diminishing OS, reducing the incidence and severity of GvHD, and preventing drug-resistant bacterial colonization and virus infections [75–77]. The microbe-derived SCFA butyrate and propionate can effectively expand Foxp3$^+$ Tregs through upregulation of GPRs expression, thus effectively inhibiting the occurrence of GvHD and promoting immune remodeling [20, 78]. Oral administration of *Bacteroides fragilis* has a

beneficial effect on the preservation of intestinal integrity and reduces inflammatory cytokine levels by increasing SCFAs, IL-22, and Treg cells [79].

5.4. Oxidative Stress and the Development of aGvHD. Inflammation is a key driver of GvHD; longstanding inflammatory conditions could result in increased oxidative stress. Leukocyte filtration induced by intestinal inflammation results in superoxide production by NADPH oxidase-1, increasing cellular ROS [36]. During an allogeneic immune response, the translocating intestinal flora activates neutrophils, the largest human leukocyte population. The neutrophil infiltration could amplify the tissue damage and contribute to GvHD in the manner of producing ROS. Selective NOX2 deficiency in neutrophils impairing ROS production led to lower levels of tissue damage, GvHD-related mortality, and effector phenotype T cells. *Enterococcus faecalis* is a commensal microorganism of the human intestinal tract that produces substantial extracellular superoxide ($O2^-$) and derivative ROS such as H_2O_2 and hydroxyl radical, through autoxidation of membrane-associated demethylmenaquinone. The predominance of *Enterococcus faecalis* in GvHD patients was confirmed in metagenomic analysis of fecal microbiome [15]. Excessive ROS produced by *Enterococcus faecalis* could increase DNA damage in colonic epithelial cells and thus may contribute to active GvHD [37, 80].

The levels of NO and its metabolites increase in mice with GvHD, which may play a role in the pathogenetic mechanism of GvHD. Treatment with NO synthesis inhibitor significantly reduces the levels of NO production and bacterial translocation across the intestine, abrogates GvHD-associated enteropathy, and reduces lymphocytic infiltration in the intestinal epithelium, as a result, prolonging the survival of rats with GvHD [81, 82]. As we mentioned above, intestinal injury plays a pivotal role in the development of acute GvHD by providing a portal of entry for Gram-negative bacteria and LPS to enter the host tissues. Ellison et al. reported that LPS injection can consistently induce intestinal epithelial cell apoptosis in graft-versus-host mice triggering mucosal macrophages to release NO, and macrophage-derived NO is the principal mediator of intestinal injury in GvHD [83]. The released NO compromises the integrity of the intestinal epithelium and makes it more permeable to endotoxin. As this occurs, a vicious cycle of intestinal epithelial injury is established in which more endotoxin triggers the release of more NO, and so on [84].

On the other side, oxidative stress can intensify inflammatory responses. Damage of oxidative stress results in oxidized proteins, glycated products, and lipid peroxidation and then turns into the release of inflammatory signal molecules and peroxiredoxin 2 (PRDX2), a ubiquitous redox-active intracellular enzyme [85]. PRDX2 from LPS-stimulated macrophages can alter the redox status of cell surface receptors and allow the induction of inflammatory cascade in chronic inflammatory diseases [85]. Therefore, overproduction of oxidative stress can activate a variety of inflammatory mediators that involve in amplifying the inflammation and form a vicious circle that contributes to the GvHD development in HSCT patients. The strategies to limit oxidative stress in GvHD are highly desirable. Sofi et al. [86] reported that Trx1 is a common antioxidant enzyme that can reduce ROS accumulation in donor T cells and decrease downstream molecules including NF-κB and T-bet, which restrained the ability of T cells to activate, expand, and migrate to the target organs in response to alloantigens in vivo. The administration of human recombinant Trx1 can decrease the pathogenicity of T cells and severity of GvHD and preserve the GVL effect, which has a great translational potential in patients with hematological malignancies undergoing allo-HCT.

6. Pulmonary Complications after HSCT

Pulmonary complications (PCs) are reported in up to 70% of HSCT recipients and account for significant morbidity and mortality [25]. HSCT patients are immunocompromised after engraftment as a consequence of chemotherapy, irradiation, acute/chronic GvHD, and maturing recipient marrow. In the postengraftment period, patients are at risk of opportunistic infections by *Pneumocystis jirovecii* and cytomegalovirus. Further, patients represent increased susceptibility to infectious pneumonitis, commonly associated with respiratory viruses, including influenza, respiratory syncytial, and adenoviruses [87]. In addition, chronic GvHD (cGvHD) can also occur later in the postengraftment period where the lung involvement results in chronic obstructive or restrictive pulmonary diseases.

Several studies have reported the relationship between intestinal dysbiosis and many pulmonary diseases, such as allergic airway diseases [88], obstructive pulmonary diseases [89], lung cancer [90], and pneumonia [91]. Therefore, it is pertinent to explore the influence of gut-lung crosstalk on the occurrence of PCs in HSCT recipients. Harris et al. performed a single-center observational study on 94 patients who underwent HSCT and were previously enrolled in a protocol for 16S ribosomal RNA sequencing of the fecal microbiota. They found that low diversity and *γ-proteobacteria* dominance in the fecal microbiota (which included common respiratory pathogens) were the independent predictors for the occurrence of PC postengraftment and overall mortality [25]. One possible mechanism is that the impaired gut barrier may facilitate microbial translocation to the lungs through circulation or indirect lung injury by a microbiota-induced systemic inflammatory response, provoking alveolar inflammation and pulmonary dysfunction. Another study analyzing post-HSCT lung microbiota in humans reported that increased relative abundance of *Proteobacteria* in the lung was correlated with impaired lung function after engraftment [92]. These evidences indicate toward a disordered gut-lung axis underlying postengraftment PCs. LPS is a structural component of Gram-negative bacteria and was shown to cause innate immune activation, accumulation of alloreactive T cells, and histologic damage by interacting with TLR4 in allo-HSCT models. Treatment with a TLR4 antagonist could protest against transplant-related lung injuries after HSCT [93]. This research confirmed the role of LPS in promoting the development of alloimmune lung injury after HSCT independent from systemic GvHD in

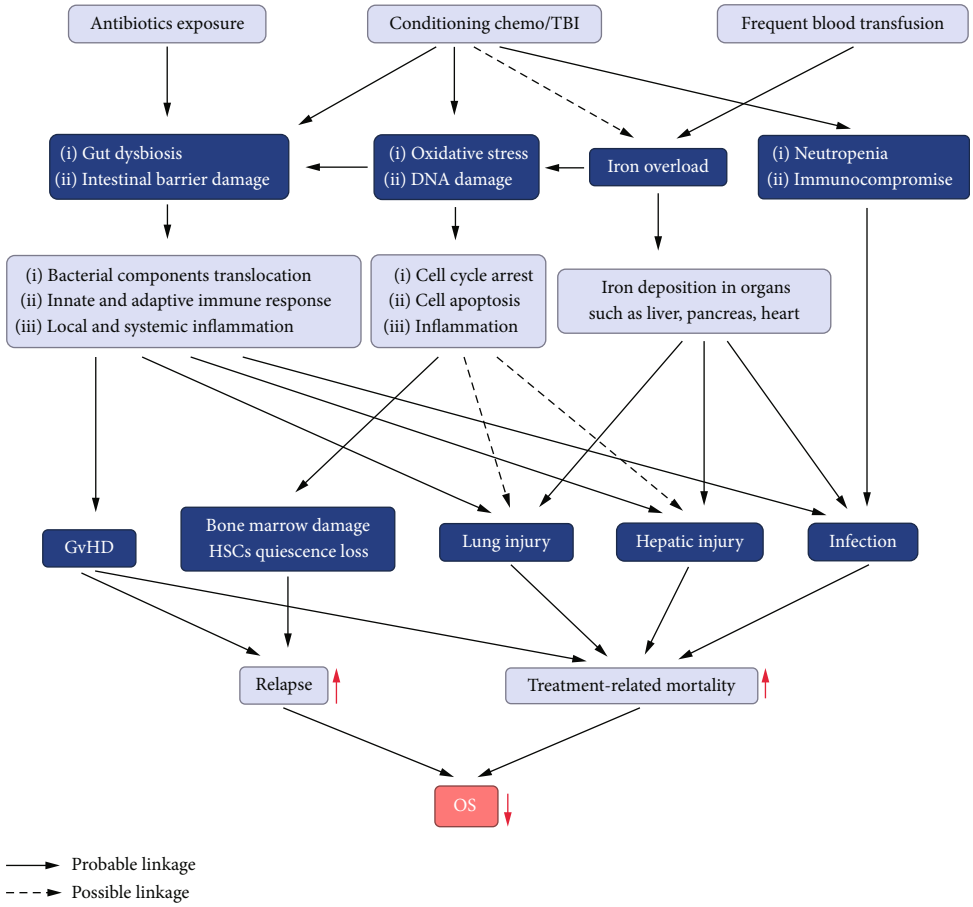

Figure 3: The interplay between intestinal dysbiosis and oxidative stress as well as the transplant-related complications. The interaction between intestinal dysbiosis and oxidative stress caused by preengraftment conditioning and prophylactic antibiotics exposure in this picture. These pathogeneses contribute to different HSCT-related complications such as GvHD, BSI, HSC dysfunction, pulmonary/hepatic injury, and infections which are leading cause of relapse and treatment-related mortality that affect the OS of HSCT. HSCT: hematopoietic stem cell transplantation; GVHD: graft-vs.-host disease; BSI: bloodstream infection; HSCs: hematopoietic stem cells; OS: overall survival.

the allo-HSCT model without systemic GvHD. On the other side, the microbial-derived metabolites of SCFAs have the ability to modulate host inflammation and promote immune tolerance against various bacterial and viral infections. HSCT patients with higher levels of SCFA-producing microbial communities were fivefold less likely to develop the pulmonary virus infection with lower respiratory tract infection, independent of other factors (adjusted HR = 0.22, 95% CI 0.04-0.69) [94]. Restoring the balance of endogenous gut microflora may play a role in the treatment of postengraftment PCs by elevating SCFA production.

OS may also play an important role in the pathogenesis of lung injuries, such as IPS and lung fibrosis, following HSCT. The lung is especially susceptible to oxidative damage because it has the largest endothelial surface area in the body, making it vulnerable to circulating toxins. Gut *Lactobacilli* and *Bifidobacterium* possess the ability to convert nitrate and nitrites into NO, making the gut epithelia a rich source of NO [95]. Similarly, *Streptococcus* and *Bacillus* produce NO from L-arginine using nitric oxide synthase. A higher pulmonary concentration of NO combined with superoxide results in the formation of peroxynitrite, a strong oxidant that can oxidize a number of biomolecules including tyrosine-containing proteins, resulting in nitrotyrosine formation. An increased concentration of exhaled NO in the lower respiratory tract and increased nitrotyrosine formation in the alveolar fluid following HSCT were identified as potential markers of IPS [96]. IPS is characterized by noninfectious diffuse lung injury associated with a high-dose chemotherapy regimen (BCNU, cyclophosphamide, and cisplatin) and the incidence of GvHD after HSCT. Murine models of IPS have shown that the conditioning regimen causes lung injury beginning with substantial OS, which further promotes intense monocytic cellular infiltration and macrophage activation. An increased alveolar macrophage population in the epithelial lining fluid has a significantly higher oxidative burst, which may further exacerbate lung inflammation and widespread alveolar injury [97]. In addition, increased ROS and cellular DNA damage in pulmonary

fibroblasts are key events in the progression of pulmonary fibrosis, which is frequent post-HSCT [98].

7. Sinusoidal Obstruction Syndrome

Hepatic SOS, also known as venoocclusive disease, is a potentially life-threatening complication that occurs in 13% of HSCT patients, belonging to a group of diseases increasingly identified as transplant-related, systemic endothelial diseases [99]. Severe SOS results in multiorgan dysfunction with a mortality rate > 80%. The SOS primarily insults both sinusoidal endothelial cells and hepatocytes in zone 3 of the hepatic acinus, which can be triggered by multiple factors including the toxicity of the conditioning regimens [100], cytokine cascade, microbial endotoxins, immune and alloreactivity.

Elevated oxidative stress in HSCT patients may be involved in the development of SOS. (-)-Epicatechin is a natural flavonol that was found to obviously enhance liver GSH levels and reduce the increased ROS amounts, thus reversing liver oxidative injury and attenuating SOS by activating nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway [101]. As mentioned above, iron accumulation promotes the production of ROS via the catalytic activity of free iron. As the liver is one of the organs in which iron preferentially accumulates, oxidative stress promoted by iron overload in livers after conditioning regimens might be attributed to triggering and exacerbating hepatic injury including SOS in HSCT patients [102]. Yeom et al. demonstrated that ROS levels of the murine liver increased according to cumulative iron dose and correlations with pathologic score for SOS, including sinusoidal hemorrhage and endothelial damage, in HSCT mice with no significant differences between the syngeneic and allogeneic groups [103]. Mitigating oxidative stress with antioxidants has shown protective effects on SOS-related liver injury in many studies [101, 104, 105]. Sesame oil has antioxidant properties that offer better protection against increased blood pressure, hyperlipidemia, and lipid peroxidation by increasing enzymatic and nonenzymatic antioxidants. Inhibiting OS with prophylactic sesame oil prevents the rounding up of sinusoidal endothelial cells and thus attenuates SOS in murine [105].

Preclinical studies suggest that microbial products translocated across impaired intestinal barriers may participate in the pathogenesis of endothelial damage, interfering with procoagulant and fibrinolytic endothelial responses [106]. LPS in especially activates various signaling mechanisms in endothelial cells, ultimately leading to cellular dysfunction and injury [107]. A retrospective case-control study in allo-HSCT pediatric patients conducted by Masetti et al. reported that having healthy gut microbiota characterized by a high diversity and richness of beneficial microorganisms in the pretransplant period is associated with a reduced occurrence of SOS. The disrupted intestinal barrier with depleted beneficial taxa and low production of beneficial SCFAs could lead to greater translocation of microbial molecules. The microbial endotoxin, particularly LPS, translocates across impaired intestinal barriers, reaches the liver sinusoid through the portal vein, and participates in endothelial damage by activating various signaling mechanisms, including NF-κB and p38 MAPK [107, 108]. LPS-induced nitrooxidative stress may also participate in damaging liver microcirculation. The iNOS expression was increased in livers of the LPS-injected mouse group, evidenced by increased liver dihydroethidium staining and increased liver protein nitrotyrosination which can be blunted by the effect of iNOS inhibition [109]. These endothelial changes lead to the narrowing of the central vein lumen and obstruction of the blood flow. This is followed by the organization of subintimal edema and deposition of additional collagen. Thickened collagen cuffs surrounding the central veins characterize chronic SOS.

8. Conclusion

Intestinal dysbiosis and OS caused by preengraftment conditioning and prophylactic antibiotics result in different HSCT-related complications such as BSI, GvHD, pulmonary injury, and hepatic injury, which are the leading causes of adverse outcomes after HSCT. Disturbance in intestinal microbiota is due to the conditioning regimen, antimicrobial administration, and iatrogenic immunocompromisation in patients undergoing HSCT. Preengraftment conditioning affects the intestinal mucosa due to increased OS and DNA damage in the intestinal epithelial cells. Translocation of commensal and pathogenic bacteria into the bloodstream through impaired intestinal barriers may induce BSIs and host immune responses. Excessive translocation of microbial components leads to allogeneic donor T cell activation and a series of cytokine storms, greatly enhancing the immune response to the recipient antigen and launching cytotoxic attacks on the recipient target cells, which are positively related to the GvHD occurrence. Gut bacteria and their endotoxins can cause pulmonary and liver inflammation and infection through hematogenous dissemination and are also related to pulmonary infections, IPS, and SOS post-transplantation. Several studies have reported antibiotic-mediated decrease in gut bacterial diversity. Further, strategies are also described for restoring the intestinal flora using fecal microbial transfer and probiotics in an aim to manage transplant-related complications and improve clinical outcomes (Figure 3). The immunoregulatory effects of microbial metabolites on SCFAs have also been confirmed in GvHD. Removing the disturbance of redox balance to antioxidant supplements and OS depletion by reducing preconditioning intensity and decreasing iron accumulation has beneficial effects in the management of GvHD, infections, and organ injury in HSCT patients. However, further studies are needed to elucidate the role of intestinal flora-mediated OS in the pathology and treatment of HSCT-related complications, which may provide additional understanding of the pathways employed by gut microbiota in mediating the process of HSCT-related complications.

Abbreviations

HSCT: Hematopoietic stem cell transplantation

HSCs: Hematopoietic stem cells
GvHD: Graft-versus-host disease
IPS: Idiopathic pneumonia syndrome
SOS: Sinusoidal obstruction syndrome
ROS: Reactive oxygen species
OH: Hydroxyl radical
H_2O_2: Hydrogen peroxide
NO: Nitric oxide
OS: Oxidative stress
SCFAs: Short-chain fatty acids
AhR: Aryl hydrocarbon receptor
Treg: Regulatory T
Foxp3: Forkhead box protein P3
MDRO: Multidrug-resistant organisms
DAMPs: Damage-associated molecular patterns
MAPK: Mitogen-activated protein kinase
NF-κB: Nuclear factor kappa-B
CTX: Cyclophosphamide
BCNU: Carmustine
BSI: Bloodstream infection
IL-1β: Interleukin-1β
PAMPs: Pathogen-associated molecular patterns
GPRs: G protein-coupled receptors
TNF: Tumor necrosis factor
Th: T helper
MHC: Major histocompatibility complex
MAIT: Mucosa-associated invariant T
GVL: Graft-versus-leukemia
FMT: Fecal microbiota transplantation
PCs: Pulmonary complications
LPS: Lipopolysaccharide.

Ethical Approval

This article does not contain any studies with human participants/animals performed by any of the authors.

Conflicts of Interest

All the authors declare that they have no conflict of interest.

Authors' Contributions

Mingxuan Chi, Tao Jiang, and Xing He were involved in writing the article. Haoyu Peng, Yunlong Li, Qing Nian, Jiong Zhang, Li Wang, Kuai Ma, and Chi Liu critically revised the manuscript. All authors read and approved the final manuscript. Mingxuan Chi, Tao Jiang, and Xing He contributed equally to this work.

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