Review Article

Nutrition and the gut microbiome during critical illness: A new insight of nutritional therapy

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Abstract

Changes in the microbiome in response to environmental influences can affect the overall health. Critical illness is considered one of the major environmental factors that can potentially influence the normal gut homeostasis. It is associated with pathophysiological effects causing damage to the intestinal microbiome. Alteration of intestinal microbial composition during critical illness may subsequently compromise the integrity of the intestinal epithelial barrier and intestinal mucosa absorptive function. Many factors can impact the microbiome of critically ill patients including ischemia, hypoxia and hypotension along with the iatrogenic effects of therapeutic agents and the lack of enteral feeds. Factors related to disease state and medication are inevitable and they are part of the intensive care unit (ICU) exposure. However, a nutritional intervention targeting gut microbiota might have the potential to improve clinical outcomes in the critically ill population given the extensive vascular and lymphatic links between the intestines and other organs. Although nutrition is considered an integral part of the treatment plan of critically ill patients, still the role of nutritional intervention is restricted to improve nitrogen balance. What is dismissed is whether the nutrients we provide are adequate and how they are processed and utilised by the host and the microbiota. Therefore, the goal of nutrition therapy during critical illness should be extended to provide good quality feeds with balanced macronutrient content to feed up the entire body including the microbiota and host cells. The main aim of this review is to examine the current literature on the effect of critical illness on the gut microbiome and to highlight the role of nutrition as a factor affecting the intestinal microbiome-host relationship during critical illness.

Keywords: Critical illness, gut microbiome, nutrition, paediatrics

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INTRODUCTION

Changes in the gut microbiome in response to environmental influences can affect the overall health.[1-3] Critical illness is considered one of the major environmental influences that can impact the gut environment.[4] It is associated with pathophysiological effects causing damage to the intestinal microbiome. These include ischemia, hypoxia and hypotension along with the iatrogenic effects of therapeutic agents and the lack of enteral feeds.[5-7] As a result of alterations to the intestinal microbial composition, the integrity of the intestinal epithelial barrier and intestinal mucosa absorptive function is compromised.[8-12]

Generally, the intestinal microbiome of critically ill children and adults is characterised by low diversity.[13,14] Critically ill children and adults appear to be rapidly colonised with

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opportunistic pathogens.[14,15] Besides, a loss of intestinal anaerobic bacteria has been frequently detected during critical illness, and accordingly the colonic degradation capacity of undigested carbohydrates into lactic acid and short-chain fatty acids (SCFAs) may be affected.[16-19] The interaction between the host and intestinal microbiome is highly relevant to pathophysiology and outcomes in severe and critical illness. Damage to the intestinal mucosal lining in severe disease may lead to the translocation of bacteria or their fragments into the bloodstream and this may contribute to inflammation, sepsis, multi organ failure Multi-organ failure (MOF) and death.[20-22] The depletion of the normal gut microbial population and metabolites and alterations to the intraluminal gut environment is associated with adverse outcomes in critically ill adults.[23] Indeed the gut is seen as an important driver of organ failure in critical illness[24] [Figure 1].

FACTORS AFFECTING INTESTINAL MICROBIOME DURING CRITICAL ILLNESS

Disease state

The intestinal microbiome is altered in response to the pathophysiological effects of critical illness. The pro-inflammatory stimulation appears to influence the tight junctions between enterocytes and results in increased epithelial permeability, the infiltration of luminal antigens and the induction of intestinal inflammation.[20] Intestinal inflammation and hypoxia have a significant impact on modulating the gut microbiome and microbiota composition during critical illness.[8,9] Both promote a shift from commensal anaerobes to opportunistic pathogens.[8,9] Furthermore, intestinal inflammation alters the responses of gut hormones and neurotransmitters and accordingly impacts gut motility.[12,25] It was speculated that inflammation suppresses the expression of certain hormones such as peptide YY (PYY) by mature endocrine cells, resulting in impaired gut motility.[26] The activation of inflammatory cytokines and increased levels of luminal catecholamine has also been shown to promote the growth of pathogenic species.[27,28] Impaired mucosal immunity and decreased immunoglobulin A (IgA) production are other features of acute illness and are associated with decreased ability to eliminate intestinal pathogens.[27]

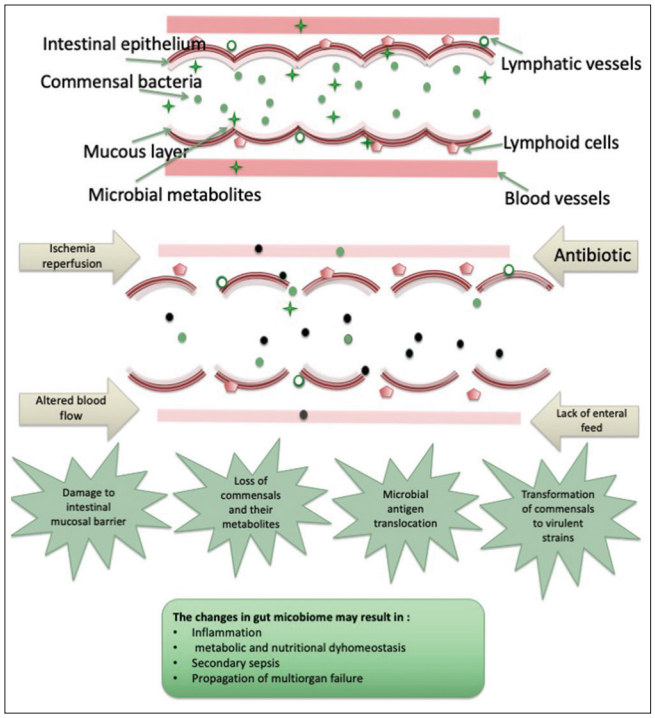

Figure 1: A summary of the changes that occur in the gut microbiome during critical illness. In response to acute insult, factors such as reperfusion, antibiotic therapy and the lack of enteral feed result in damage to the intestinal barrier and changes in microbial composition. Alterations to the gut microbiome are strongly related to the exacerbation of the inflammatory response, metabolic dysregulation sepsis and the propagation of multiorgan failure

Medication

The pharmaceutical agents commonly used in intensive care unit (ICU) such as antibiotics, inotropic drugs and vasopressors are known to impact human microbiota.[7-9,29,30]

Critically ill patients are frequently treated with antibiotics. It has been estimated that the total antibiotic consumption in ICU settings is nearly ten times greater than in general hospital wards.[31] Several studies have recorded profound changes in gut microbial communities following the administration of antibiotic treatment, which can subsequently result in important functional alterations of the gut microbiome and increase susceptibility to gastrointestinal infections.[32,33] The effect of antibiotic exposure on gut microbiota has been widely investigated. The main phyla influenced by antibiotic treatment appear to be *Actinobacteria*, *Bacteroidetes*, *Firmicutes* and *Proteobacteria*.[34-36] In a study conducted on antibiotic-treated infants, a massive reduction in total bacterial densities was observed after antibiotic treatment, accompanied by delayed colonisation by beneficial species such as *Bifidobacteria* and *Lactobacilli*, and induced colonisation by antibiotic-resistant strains.[37] The findings from these studies could explain the high prevalence of nosocomial infections with increased antibiotic consumption in critically ill patients.[38]

The alteration in the balance of gut microbiota following antibiotic treatment could be short-term or may last for a longer period. An example of the long-lasting effect of antibiotic use is reduced colonisation resistance against some pathogens such as *Clostridium difficile*.[34] As this population often receives extensive antibiotic treatment,

it may, in addition to the functional loss of commensal species, affect the prevalence of antimicrobial-resistant genes within the intestinal microbiome.

Other therapeutic agents used in ICU settings are also known to impact the intestinal microbiome, including inotropic drugs that promote the growth of pathogens.[29,30] Vasopressors like calcium-channel blockers have recently been shown to inhibit the growth of commensal bacteria, however, the exact mechanism has not been established yet.[7]

Nutrition

Nutrition has an indirect effect on the gastrointestinal function of the host and thereby on health, mainly by influencing the composition and activity of the human gut microbiota. It is considered one of the major determinants of the intestinal microbial composition. The route of feeding greatly affects the gut microbial population.[39,40] Enteral nutrition (EN) helps to maintain the immunological function of the gastrointestinal tract; it decreases bacterial translocation and accordingly blunts the systemic inflammatory response.[41,42] Besides, early compared to delayed enteral feeding is associated with less bacterial translocation and better mucosal integrity.[43,44] In contrast, bowel rest, as associated with total parenteral nutrition (PN) or delayed EN, results in gastrointestinal mucosal atrophy, which compromises the integrity of the mucosal barrier and enhances exposure to bacteria and endotoxins.[41,45,46] The composition of EN is also known to greatly influence the colonisation, maturation and stability of the intestinal microbiota.[47] The effect of the dietary component on intestinal microbiota varies; it may promote the growth of opportunistic microbes while other dietary factors could endorse beneficial microbes.[48]

Dietary fibre is the primary energy source for most commensal species and, therefore, can directly impact their growth.[49] It is also the main substrate for the microbial production of important bacterial metabolites known to influence the host's health.[50] The effect of fibre supplementation on gut microbiota has been widely investigated in healthy subjects, and data showed that the main species influenced *were Bifidobacteria*, *Lactobacilli*, *Faecalibacterium prausnitzii* and *Roseburia*.[51-55] Nutrition status is also an important factor determining the diversity of the intestinal microbiome.[56] Therefore, the state of energy deficit, particularly during the acute phase of illness, might have a profound effect on the gut microbiota and environment.

CONTRIBUTION OF INTESTINAL MICROBIOTA TO THE HOST HEALTH

The gut microbiota use ingested dietary components (carbohydrates − mainly resistance starch, proteins and lipids) to generate energy for cellular processes and growth.[57] During the process of utilising these substrates, the microbiota produces several metabolites that influence host health and metabolism.[56,57]

Macronutrient metabolism

Preclinical data and animal studies have suggested possible mechanisms of the contribution of intestinal microbiota to the regulation of macronutrient metabolism.

Carbohydrates

The fermentation of polysaccharides (fibre) by anaerobic bacteria leads to the production of SCFAs, which are utilised by the host. Colonic epithelial cells derive up to 70% of their energy from the oxidation of butyrate.[58] The microbial gluconeogenesis from propionate reduces hepatic gluconeogenesis and promotes energy homeostasis.[59,60] Gut microbiota is also known to regulate glucose metabolism through the stimulation of glucagon-like peptide-1 (GLP-1) and PYY hormone secretions from intestinal L-cells.[61,62]

Protein

Gut microbiota contributes to host nitrogen balance through de novo synthesis of amino acids and intestinal urea recycling. Studies with radiolabelled tracers suggest that gut microbes synthesise nearly 20% of circulating threonine and lysine in healthy adult humans.[63] The intestinal microbiota also contributes to host nitrogen balance by participating in urea nitrogen salvaging.[10] Elevated urease expression in gut microbes results in the metabolism of urea in the gastrointestinal (GI) tract into ammonia and carbon dioxide. Some of the ammonia can be utilised for the microbial synthesis of amino acids. More importantly, the nitrogen generated during this process can re-enter the host circulation and serve as a substrate for synthetic processes.[10] Reduced urea recycling has been reported in germ-free animals and humans receiving antibiotic therapy.[64,65] Therefore, the state of negative nitrogen balance frequently observed during critical illness could be partially attributed to disturbances in the gut microbiome, which impacts the intestinal urea recycling process.

Lipids

The impact of dietary lipids on the microbiota in critically ill patients has not yet been established. However, preclinical studies in animal models indicate that the intestinal microbiota regulates fat metabolism by suppressing

the activity of a circulating inhibitor of lipoprotein lipase (LPL).[66] This results in increased levels of circulating LPL, which stimulate hepatic triglyceride production and promote the storage of triglycerides in the adipocyte.[66-68] Suppression of LPL inhibitors is promoted by intestinal microbiota through transcriptional suppression of the intestinal epithelial gene encoding for LPL inhibitors.[66] Abnormalities in lipid metabolism commonly observed during critical illness could be also related to the disturbance in the functional capacity of the gut microbiota.

Short chain fatty acids (SCFAs)

SCFAs arising from the anaerobic bacterial metabolism of indigestible dietary fibre in the colon are beneficial to the host health. SCFAs support the integrity of the gut barrier by regulating the release of mucus by colonic cells and acting as a fuel source to colon cells. They also have immune-modulating activity and are involved in the release of gut hormones.[69,70] The principal SCFAs seen in the colon are acetate, propionate and butyrate. SCFAs are depleted in adults with a critical illness, often due to the effect of the acute insult and other environmental factors on SCFAs-forming species.[16-19,71,72]

SCFAs as a source of energy

The bacterial formation of SCFAs enables the host to salvage some of the energy contained in dietary fibre that would otherwise be lost, while various tissues in the body can oxidise SCFAs for energy generation.[58] SCFAs are absorbed by passive diffusion across the colonic epithelium and utilised by different organs. Colonic epithelial cells derive up to 70% of their energy from the oxidation of butyrate.[50] Propionate serves as a substrate for microbial gluconeogenesis.[59,60] Acetate is used by skeletal and cardiac muscle and can also be utilised by adipocytes for lipogenesis.[73] Butyrate is metabolised primarily in the gut epithelium to yield ketone bodies or CO_2 and propionate is transported to the liver for gluconeogenesis.[10]

Physiological functions of SCFAs

Besides being used as fuel by different organs, SCFAs have other physiological functions.[74,75] For instance, butyrate appears to affect cell differentiation and protects cells from carcinogens, either by slowing growth and activating apoptosis in colon cancer cells,[76] or by upregulating the detoxifying enzymes, such as glutathione-S-transferases.[77] SCFAs also impact water absorption, local blood flow and epithelial proliferation in the large intestines.[10] SCFAs have a direct protective effect on strengthening the gut barrier in the normal colon by increasing the production of mucus by colonocytes.[78] Most importantly, SCFAs are involved in the regulation of inflammation. Generally, SCFAs exert their physiological functions by acting as signal molecules that activate target receptors in various cells and organs.

SCFAs as signalling molecules

The physiological effects of SCFAs depend on the activation of G protein-coupled receptors (GPRs).[69,79] In adipocytes, the activation of GPR43 by SCFAs results in the suppression of insulin signalling and accordingly inhibits lipogenesis and enhances glucose and lipid utilisation by the muscles. On the other hand, activated GPR41 enhances the production of leptin and activated GPR109A suppresses lipolysis.[79,80] Besides, it has been suggested that the SCFAs activation of GPR41 in adipocytes increases fatty acid oxidation and energy expenditure.[50] The expression of GPR41 and GPR43 by SCFA in the intestines promotes gut hormone secretion, which regulates energy homeostasis[61,62] [Figure 2].

SCFAs and inflammation

An important driver of MOF in critical illness is the dysregulation of innate immune pathways and the loss of balance between pro-inflammatory and anti-inflammatory mechanisms.[81] SCFAs appear to play a role in modulating inflammatory and immune responses, since they modify the migration of leukocytes to the site of inflammation, as well as modifying the release and production of chemokine.[69] The activation of GPR43 by SCFAs induces chemotaxis and regulates the degranulation of neutrophils.[79] The anti-inflammatory properties of SCFAs have been investigated in patients with inflammatory bowel diseases (IBD). In a previous study in patients with IBD, impaired butyrate metabolism was reported.[82] SCFAs, in particular butyrate, reduce inflammatory cytokine production and inflammation in the intestine through mechanisms including nuclear factor kappa B signalling.[57,83] SCFAs exert an inhibitory effect on both tumour necrosis factor-alpha (TNF-α)-mediated activation of the nuclear factor kappa B pathway and lipopolysaccharide-induced TNF-α release.[83] On the other hand, they increase the secretion of anti-inflammatory interleukin-10 (IL-10) from macrophages.[79]

Regulation of bile acid metabolism

Bile acids (BAs) are synthesised in the liver from cholesterol and stored in the gall bladder. They are released into the small intestines following food ingestion to aid the digestion process by facilitating the emulsification of dietary fats. The physiological functions of BAs in the human body are not only restricted to facilitating lipid digestion and absorption, they appear to be also involved in the overall regulation of host metabolism.[84] Recently, preclinical studies in murine and *in vitro* models indicated that BAs contribute to the

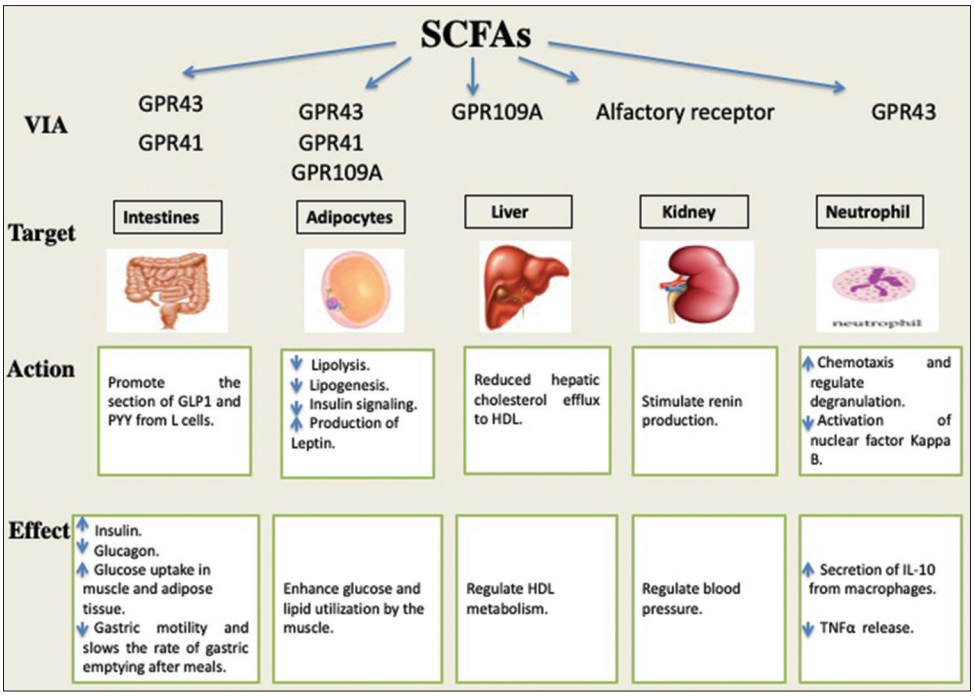

Figure 2: SCFAs as signalling molecules activating G-protein-coupled receptors. A summary of the physiological function that SCFAs exert by activating G-protein-coupled receptors in different target organs and cells. *GPR (G protein-coupled receptors)

activation of the farnesoid X receptor (FXR) and the GPR5 receptor. These receptors activate the expression of genes involved in BAs, lipids and carbohydrates metabolism as well as energy expenditure regulation.[85-87]

The human BA pool is made up of primary, secondary and tertiary BAs. The primary BAs (cholic acid [CA] and chenodeoxycholic acid [CDCA]) are synthesised in the liver, while secondary BAs are produced in the gut via the modification of primary BAs through dehydroxylation, epimerisation and oxidation. The tertiary BAs are formed in both the liver and gut microbiota via modification of secondary BAs through sulfation, glucuronidation, glucosidation and N-acetylglucosaminidation.[88-90]

Primary BAs synthesised by the liver are conjugated with taurine or glycine and during enterohepatic circulation they are then deconjugated through gut microbial action.[89] The resulting free amino acids are then metabolised by intestinal microbiota (e.g., *Bifidobacterium*) for energy supply.[91]

The intestinal microbiota possesses enzymes involved in the regulation of the BA pool such as bacterial bile salt hydrolases, bacterial hydroxysteroid dehydrogenases and 7α/β-dehydroxylase.[89] The majority of intestinal microbial species facilitate deconjugation and dehydrogenation of bile salts through the expression of bacterial bile salt hydrolases and bacterial hydroxysteroid dehydrogenases. Limited intestinal species (e.g., *Clostridium* clusters XI and XVIa, such as *C. sordellii*, *C. sordelliifell* and *C. scindens)* express 7α/β-dehydroxylase enzymes that catalyse the dehydrogenation reaction of primary BAs[89,92] [Figure 3].

TARGETED MODULATION OF INTESTINAL MICROBIOME TO IMPROVE CLINICAL OUTCOMES IN CRITICALLY ILL PATIENTS

Given the substantial clinical and experimental evidence supporting the gut-lymph hypothesis,[22,93] the targeted modulation of the intestinal microbiome has been proposed as a therapy to support gut health in critically ill patients.

The suppression of pathogenic gut bacteria was the first therapeutic line of microbiome modulation tried on critically ill patients. Selective decontamination of the digestive tract (SDD) was first introduced in the 1980s,[94] aimed at keeping the overgrowth of potential pathogens in the gut to the minimum through the administration of tailored antibiotic treatment.[27,94] Ever since, SDD intervention has been tested in many clinical trials in critically ill patients.[95-97] Although proven effective and shown to significantly reduce the rate of infections, the number of patients with MOF and mortality,[95,96,98] there remains concern about the potential risk of antimicrobial resistance.[99,100] All these data are derived from studies on critically ill adults, and paediatric-specific clinical trials

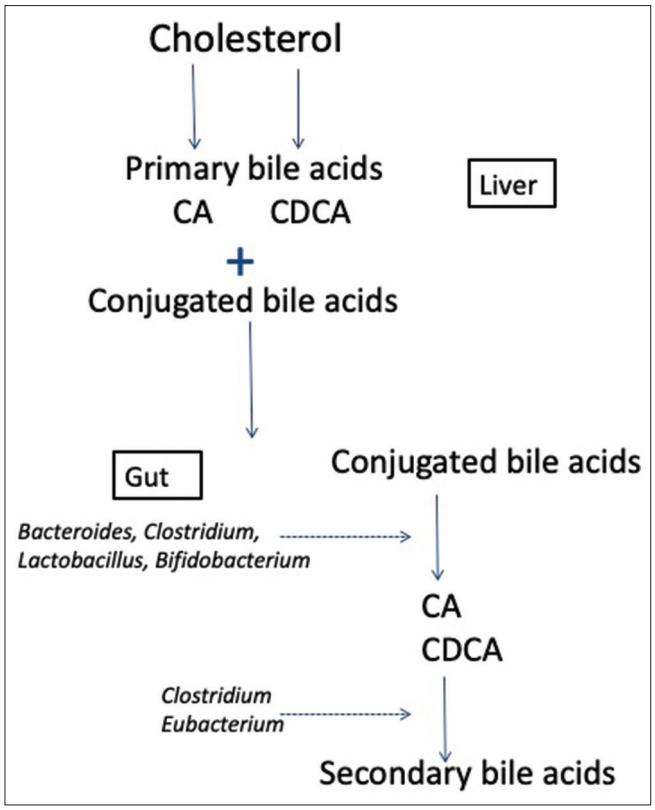

Figure 3: Regulation of bile acid metabolism by intestinal microbiota illustrating the contribution of *Bacteriodes, Clostridium, Lactobacillus, Bifidobacteria* and *Eubacterium* to the regulation of bile acid metabolism. *CA (Cholic Acid). *CDCA (Chenodeoxycholic Acid)

are absent. In a recent survey by Murthy *et al.* (2017) to determine the baseline knowledge of healthcare providers about SDD, they indicated that there is still uncertainty about implementing SDD protocols in paediatric ICUs, mainly due to concerns about antimicrobial resistance.[101]

Given the extensive vascular and lymphatic links between the intestine and other organs, it is possible that enhancing the growth of commensal bacteria and their metabolites by EN could be of systemic clinical benefit. Certain nutrients have been verified for their capacity to modulate the gut bacterial profile, such as glutamine and prebiotics (the dietary fibre that promotes the growth of beneficial bacteria). In a previous study to evaluate the effect of glutamine supplementation on gut microbial content, they reported significant changes in the composition of the gut microbiota in obese subjects.[102] As regards to prebiotics, lactulose added to infant formulas were used long enough to increase the numbers of lactobacilli in infant's intestines.[103] However, this practice has evolved with extensive research on the role of prebiotics in enteral feeds. The most common prebiotics are fructooligosaccharides and galactooligosaccharides; they have been added to several infant formulas and they demonstrated modulation of the gut bacterial population.[104,105] The use of probiotics containing *Lactobacillus* and *Bifidobacteria* species has a beneficial effect on modulating the balance of the intestinal microbiota.[103] Furthermore, using probiotics in combination with antibiotic therapy has proven to have a beneficial effect, as probiotics not only suppress gastrointestinal pathogens but may potentiate the efficacy of antibiotics by producing antibacterial factors.[33] Generally, using probiotics in clinical settings has been proven to be safe, however, they must be used with caution in certain patient groups.[106] A theoretical concern with the safety of using probiotics is that some of them may adhere to the intestinal mucosa and facilitate bacterial translocation and virulence.[107] However, Srinivasan *et al.* (2006) showed that the supplementation of probiotics in enterally fed critically ill children is safe and is not associated with any clinical complications.[106] In a recent study of critically ill adult patients, the administration of synbiotics, a combination of probiotics and prebiotics, was associated with a reduction in the rate of infections and an increase in the count of commensal bacteria, as well as SCFAs.[108] This suggests that nutritional intervention targeting the gut microbiota in critically ill patients has the potential to improve clinical outcomes.

CONCLUSION

It is crucial to understand the pathophysiological basis of the acute insult to develop new novel therapies that improve clinical outcomes of critically ill patients. It became clear that gut failure might play a role in the progression of systemic inflammation during critical illness. Therefore, the microbiome should be considered as an organ that can fail in critically ill patients and can impact other organs. Critically ill patients may be stuck in a vicious cycle of systemic inflammation and dysbiosis of the gut microbiome. Nutritional intervention could be a potential therapy to alleviate the disease state and improve clinical outcomes in this population by breaking this cycle and restoring the homeostatic state of the intestinal microbiome.

Although, nutrition is considered an integral part of the treatment plan of critically ill patients, what is missed is whether the nutrients provided are adequate and how they are processed and utilised by the host and the microbiota. The goal of nutrition therapy in critical illness should not only be limited to improve nitrogen balance, it should also be about providing good quality feeds with balance macronutrient content to feed up the entire body including the microbiota and host cells. Nutritional interventions may help to maintain the commensal population and restore normal gut host

relationships. Yet no clinical trials in critically ill patients have tried targeted gut modulation by nutritional intervention. Future work should aim at personalising the care of the critically ill population and suggest ways to manipulate the body's response to severe illness to restore the homeostatic state.

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Conflicts of interest

There are no conflicts of interest.

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