Microbiota

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The specifications of microbiota in Medicine/Neonatology

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In Medicine, considering the near environment, the microbiota is widely a new and developing concept, as new advances are noticed and performed. To give even to a preterm infant is not easily acceptable aspect. But for the gastro-intestinal flora reconstruction is essential. This Chapter is a short look on Microbiota in Medicine, especially considering on the Neonatology Perspective.

Mİcro organisms are in general the contrary to human as causes diseases. Until we confirm that, they are a protective and useful to our Human body, we try to learn them and by having knowledge, increasing the admiring to them.

Each micro-organism has special effect/duty, not to be considered as the same, or similar.

Note the concept is when, why, where and by whom arguments, that means a philosophy on Microbiota. This Unit is somehow indicating some thought on them.

The microbiota is discussed under the specifications in general, at the newborn period, especially for preterm infants. This perspective, not only considering the literature on Neonatology and Probiotics, this is a general and specifications of the microorganisms.

Outline
The specifications of microbiota in Medicine/Neonatology

Aim: The popular, commercial microbiota will be confirmed, and discussed their specialties and the evidence on health, already administrating at the Neonatology.
Groundings: By Wikipedia and other Web researches the Science/Evidence Based Medicine concept the probiotics are confrontation of the status.
Introduction: In the Nature, there will be no spare of livable organisms. The versus of physiological intestinal flora and pathological flora is discussed under Medical concept.
Proceeding: The immune reactions as Imbalance (Response) and the confirmation of the probiotics are considered under the literature.
The microbiomes and the evidence of health is further consideration.
Results: Some aspects s; a) the gut flora and host reactions, b) their using in certain cases, c) the result at preterm infants/compromised immune system, d) the causative agent of bacteremia.
Conclusion: Microbiota is a physiological flora, the pathogens are known causative for the diseases as sepsis, the preference of the flora microorganisms is discussed.
Key Words: Probiotics, Neonatology, the benefit and warning of microbiota.

Özet
Tıpta / Neonatolojide Kullanılan Mikrobiyota özellikleri

Amaç: Genel Mikrobiyomların özelliklerine göre sağlık etkileşimleri bu Bölümde irdelenmektedir.
Dayanaklar: İnternet ve Wikipedia kaynaklı inceleme ele alınmaktadır. Konu Kanıta/Bilime Dayalı Tıp Temelinde ele alınmaktadır.
Giriş: Doğada boş bir alan olmadığı, hemen her alanda canlı ve mikroorganizmaların olduğu gözlenmektedir. Bağırsaklarımızdaki floranın da fizyolojik veya patolojik oluşması konusu ele alınmaktadır.
Yaklaşım: İnflamasyon ve savunma sistematiği çeşitli mekanizmalar üzerinde ele alınarak (Imbalance/Dengesizlik) bu mikrobiyatanın boyutu ele alınmaktadır.
Bazı konulara dikkate alınarak irdelenmektedir. Bunlar; a) barsak florası ve konakçı reaksiyonları, b) bazı konularda Mikrobiyomların kullanılması, c) immün yetmezlikler olanlar/prematürelerde kullanılması, d) bakteriyemi nedeni olarak probiyotikler.
Elde Edilenler/Sonuç: Probiyotikler fizyolojik flora olduğu dikkate alındığında, patojenlerin temel hastalık yaptığı ele alınarak, tercih konusu olarak ele alınması irdelenmektedir.
Yorum: Fizyolojik floranın sağlanması ve desteklenmesi önemli olarak ele alınmaktadır.
Anahtar Kelimeler: Probiyotikler, Neonatoloji ve Kinik kullanımı, mikrobiyota konusundaki uyarılar.

Microbiota

Wikipedia

Int his Chapter the microbiota commonly used and their actions in general is indicated. The microbiomes are some spp have special biological functions. Not to be taken all as same. They have common functions and altogether each micro-organism has special, unique functions, that is indicated below.

Contents

First the commercial microbiota will be confirmed, to be discussed.

1. **CVS Health, Maximum Strength, Probiotic, dietary Supplement**
   - *Bifidobacterium breve*
   - *Bifidobacterium longum*
   - *Lactobacillus acidophilus*
   - *Lactobacillus casei*
   - *Lactobacillus parcasei*
   - *Lactobacillus plantarum*
   - *Lactobacillus rhamnosus*
   - *Lactobacillus lactis*
   - *Streptococcus thermophilus*
2. **Culturelle, Digestive Health**
   - *Lactobacillus rhamnosus GG*
3. **Ready to use powder as: Kefir**
   - Mesofil homofermentatif : (*Streptococcus lactis subsp. cremoris, S. durans*), ve
   - Lactobacilli: (*Lactobacillus brevis, L. delbrueckki subsp. bulgaricus, L. kefir, L. casei*.
   - *Leuconostic spp : Leuconostoc mesenteroides subsp. (Dextranicum*).
   - Fungi: (*Kluyveromyces marxianus subsp. marxianus, Torulaspora delbrueckii, Saccharomyces cerevisiae, Candida kefir*)
4. **The microbiological analysis of Kefir granules**;
   - Lactobacilli: (*Lactobacillus caucasicus, L. casei, L. plantarum, L. acidophilus, L. kefiranofaciens, L. cellobiosus, L. bulgaricus, L. helveticus spp. jugurti ve L. lactis, lactococcal spp. and Lactococcus lactis spp. lactis, L. lactis spp. lactis biovar diacetylactis, L. lactis spp. cremoris, Streptococcus thermophilus, L. filant*),
   - Leuconostoc spp (*Leuconostoc dextranicum, L. mesenteroides ve L. kefir*)
   - Streptococcus durans
5. **Kefir and other probiotics**;
   - *Kluyveromyces lactis, K. marxianus, K. fragilis*
   - Torula kefir
   - *Saccharomyces kefir and Saccharomyces cerevisiae, S. carlsbergensis*

4) **Probiotic Ready to make Yogurt (Name: Bizim-Doğadan1**)
   1. *Lactobacillus delbrueckki ssp bulgaris, L. bacillus acidophilus, L. Bacillus rhamnosus, L. Bacillus plantarum*
   2. *Streptococcus thermophilus*
   3. *Bifidobacterium animals spp lactis*

5) **Ready to use probiotic for yogurt (Name: Bizim-Doğadan2)**
   1. *Lactobacillus delbrueckki ssp bulgaris*

2. *Streptococcus thermophilus*

6) **Babyfor Combiyotic Yogurt Probiotics (Name: Bizim-Doğadan3)**
   1. *Lactobacillus delburueckki ssp bulgaris*
   2. *Streptococcus thermophilus*
   3. *Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium bifidum, L. parcasei*

Some Probiotics at the Marked for Newborn infants

1) Probien (400 mg, 30 vegetarian capsules, totally 10 billion colonies)
   1. *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Lactobacillus rhamnosus,*
   2. *Bifidobacterium Longum, Bifidobacterium bifidum, Bifidobacterium infantis*
   3. *Streptococcus thermophilus*
   4. İnülin
2) Kaleidon (1 drop, 10^6, K30; $3x10^6$, K60; $6x10^6$, capsule; $6x10^6$)
   1. *Lactobacillus rhamnosus GG*
3) Biogaia (5 mL, 30 vegetarian capsules, totally 10 billion colonies)
   1. *Lactobacillus acidophilus*
4) Biober (400 mg, 2x1 when starving, vegetarian capsules, totally 10 billion colonies)
   1. *Lactobacillus acidophilus*
   2. *Bifidobacterium breve*
   3. *Inulin*
5) Bioflor (400 mg, 30 vegetarian capsules, totally 10 billion colonies)
   1. *Saccharomyces boulardii*
   2. Lactobacillus Acidophilus
   3. *Lactobacillus casei*
   4. *Bifidobacterium bifidum*
6) Maflor, Fflor, Reflor, Oroflor, Diyacure
   1. *Saccharomyces boulardii*
7) Gynoflor, Colinox, Gynophilus, Maflor (Vaginal)

General Perspective

Wikipedia

In the Nature, there will be no empty area, the sterility is so rare and restricted at some places. Even at very hot springs, some kind of bacteria or algae can survive. Even at social bases, there is no spare of decisions if there are people.

In nature, there is no spare or empty area, all are filled with living organisms. In desert, it is scarce but not empty. The most crowded place is the Human body, at the outside, skin, the inside, gastro-intestinal system full of microorganisms. Disinfection and even some sterilizations procedures, cause great harm, so antibiotics must be used for a target of specific one, leading the disease, causative of the illness, and other flora try to be in safe. Bombing and killing all the city is not an aim at the war, only the terroristic attacks must be stopped and destroyed. Thus, we must discriminate the causative agents to disease and probiotic for natural flora, healthy environmental ones.

Therefore, we must consider the microbiota/the microorganisms, sharing the same body/physique as;

- A commensal, common body be on, non-harmful neighborhood, friendly together, coexistence with the physical structure/body.
- A mutualistic relation, a friendship, work together, with the human body
- A symbiotic relation, cooperative and interdependent, but, be safe for them not as parasitic confrontation
- A pathogenic probability, considering their own demands first, by sharing the body construction by egocentric considerations. The environment that they survive is differs, therefore hard to be a pathogenic, even cultured at the blood but not an indication of sepsis clinical findings, cause; pH at the blood is low for microbiomes to survive. They can only be subsisting outside of the cellular structure, not confirm abscess, so, cannot be subsist, means not a cause of a disease in human body.
- Synonymous, by gain to gain perspective, everyone needs them, their function is meaning to be alive for each one.

Immune Relation

Each organism has some relation considering immune relation, considering the outline at Web: 2001 Claus Steuernagel. That can be well thought-out as below;

1) Existence

All the covering of the body is sheltered/protected, not directly contact. Mostly the skin, the mucosa and gastro-intestinal tract covered by a layer of sebum, mucus or enzymatic secretion.

At the skin, a) the Stratum corneum; the keratin, the death, exfoliating epithelia, the sebum, the moist and the micro-organisms are first protective, that can be hardly enter. This is like a shield and have a perfect protection. The pH is somehow 5.5, means not allowed to be other micro-organisms then probiotics, ascites forming bacteria. Some relation, but not immune response configuration, just have a positive defensive act.

b) Stratum lucidum: The outer cellular layer, which contains the flora, have a transmission of the genetic codes, but not react at counter immune response.

c) Stratum spinosum: The cellular configuration mostly direct contact to cells. In order to be infective, the micro-organisms or parasites should be related at this layer. Mucosal structure directly can be contact, the protective one is the mucus, as the skin, corneum and lucidum. Peyer pack are open areas for allowing direct contact as open door, for confrontation of defensive mechanism, even with microbiomes.

Mucus: The secretion for adults as 100-150 mL/day. Mostly contains, collection materials as dust and some particles, sweet/secretion of skin glands and moisture (lipids with water), lysosomal enzymes, glycoproteins, leucocytes, secretory IgA, and micro-flora. At each cell, 275 cilia can be noticed, 3-4-micron length (nearly an erythrocyte length), by the oscillation of the cilia, 10-60 times/second, moves the mucus as 10 mm/minute. This means a continuous clearing of the mucosa. Digested in gastrointestinal tract, with saliva. Mostly important at the preterm, thus, below 32 gestational week, it is not developed as effective and efficiently.

Open virus, as a core, is more infective. The covered virus, mostly mentioned as the epithelial structure, can hardly be an infectious. Easily denaturized by the skin corneum or mucus. If the protective shield is damaged, then can be infection be occurred.

Microbiota. This means a protective guard or defender at the first line.

2) **Immune Response (IMBALANCE):** It can be grouped under this classification, by the demonstration of the mechanism.
    1) **I–Infection:** There are at least two concepts; 1) hypoxia and the cells cannot have confirmed their energy and other aspects to be in life, mitochondria swollen and lactic acidosis and later damaged and death of the cell. Apart of the apoptosis, tissue toxin, endogenic as myocardial depressed toxins, abdominal compartment syndrome and other conditions cause of liberated pathogenic ones. 2) The other agents, allergic or other micro-organisms infected the body. Microbiomes, even by reducing pH, not let others to be colonized.

       The encountered mechanisms are;

       a) ATP, Adenosine, Inosine, Hypoxanthine, and reperfusion leading to reactive oxygen metabolites, mucosal damage, ischemia/hypoxia, b) translocation of bacteria and toxins, c) TNF, IL-1, LTA (lipoteichoic acid, immunoglobulins neutralize endotoxin (LPS), and teichoic acid (LTA), anticoagulants influence the neutralizing LPS, growth of the micro-flora etc.
    2) **M-Mediator Release:** This is the presenting of the antigens, by LBP (lipopolysaccharides) and LPS with CD (for infective agents e.g. CD-14), forming TLR (toll Like receptor) intruding to neutrophil. By lkB kinase, bacterial DNA, by the action of mediators (TNF alfa, IL-1beta, IL-6, IL-8, INOS, COX-2, ICAM-1, tissue factor, IL-10, beta 2 adrenergic agonists, etc.) This is the first to try to understand, confirm the antigens, microbes, later forming the immune response, by this confirming it. Positive aids of the microbiomes at this mechanism.
    3) **B-Blood, Coagulation:** So, tissue factor influences Factor VIIa, later effect F-IXa, F-Xa, F-IIa (thrombin), then fibrin and DIC (Disseminated Intravascular Coagulation). Vit K synthesized by microbiomes, one of the positive effect.
    4) **A-Apoptosis:** But natural ending the life by Fas ligand, CD-95, FADD, caspase-8, to caspase-3 by oxygen free radicals to AIF, caspase-9 causing endonucleases at 4 stages then, apoptosis.
    5) **L-Labile, Anaphylaxis:** super-antigen, MHC II to V alfa, V beta to T cell receptor and result large amount of TNF alfa, IL-6, IFN gamma, leading to toxic shock syndrome, anaphylaxis. The destruction of the molecules and some clinical findings especially at Atopic Dermatitis they have encouraging results.
    6) **A-Antigen presentation:** MHCII, V alfa, V Beta from Th Cell, macrophage as antigen presenting Cell with IL-1 and IL-6, IL-1 beta and IFN gamma for Th cell relation, IL-2 actionable way to B-Cell, and proliferation to plasma cell. Result making antibodies IgM, IgG etc.

7) **N-Neutrophil activation:** This activating the neutrophils and endothelial destruction, transmigration and autoimmune responses.
8) **C-Complement:** This is a complex process; A) From tissue; membrane attack complex, tissue factor, chemotaxis, C5a to C5 alternative pathway, B) iC3b, thus, IgM prevents endothelial damage, C3bH, C3b, C3 hemolysis, C) CRP, immunoglobulins activate the classical pathway, C1, and later C3 and hemolysis.
9) **E-Effects on Tissues:** This is the direct effect of the agent, microbes; streptococcus direct tissue invasion, Gram negatives tissue necrosis, Staphylococcus forming abscess. Diagnosis can be indicated as pneumonia, urinary tract infection etc. thus, should also be confirm the etiologic agent, to fight, you should know the enemy to fight, the MIC (Minimal Inhibitory Concentration) value.

3) **Tissue Reaction Phases (FUNCTIONAL):**
   1) **F–Functional variations;** Biological variation: Variations between the gestational ages and infants
   2) **U-Unacceptable adaptation;** Physiological adaptations try to control: Adaptation mechanisms, stimulus and feedback forced to control the body.
   3) **N-Nondestructive disturbances;** Functional disturbance: Increase in respiration, deep breathing, heart rate etc. No any injury. Metabolic activity increases
   4) **C–Compensation Period;** Compensation: Compensatory phase of acidosis and alkalosis. Metabolic problems.
   5) **T–Tissue Reaction Started;** Reaction of tissues started: Vasoconstriction, pooling, interstitial edema, central flowing of blood and systemic inflammatory reactions started.
   6) **I-Impairments noticed;** Disturbances begin Cellular functions will be delayed, halted, ineffective and reactive states (e.g. Hypoxic Ischemic Encephalopathy (HIE) begin.
   7) **O-Oxidative stress/Degeneration;** Degeneration Vacuolar, hydropic cells and vazogenic edema develops. pathological findings are noticed. Changes in mitochondria
   8) **N-Noticeable findings;** Clinical inflammation reactions are noticed: Fever, swelling, pain, etc. are encountered.
   9) **A-Abnormal Tissue Reactions;** Tissue reactions Tissue reactions, degenerations, hemorrhages, scleroderma, cytostatic edema, Graft Versus Host, fibrosis.
   10) **L-Lysis, cell or tissue death;** Cell and/or tissue death Lyses of erythrocytes, necrosis

4) **Clinical Evaluation of the Findings (NOTICABLE):**
   1) **0: Negative Result**
   2) **+/-,?: Functional variations;** Biological
   3) **+:** Trigger Level, Sub Clinical, un defined situation
   4) **++:** Appearing of the disease, laboratory results are in recordable level
   5) **+++:** Brief evident, obvious level, confirmed the diagnosis

6) **++++:** Indicative result, diagnostic confirmation
7) +++++: Excess, overindulgence, mortal fact

Note

The microbiomes are not causing the immune awakening as enemy, just have a relation as; a) a non-harmful coexistence, not making reaction as antigenic aspects, b) work together with human hosts, mainly the pH differs, not to be survive in blood, but can be in intestines, c) interdependent immune benefit to the host.
The chemical and indicators are mostly noticeable from the host as non-pathogenic. Thus, quickly settle and colonized at the gut, prompting some immune actions, stimulate lymphoid tissue that in intestinal sides, responses for programming, stimulation with long lasting properties.
Microbiomes piece of some part in the activation of TLRs (toll-like receptors) in the intestines, which is PRR (pattern recognition receptor) used mainly to help repair damage and recognize dangers to the host, commonly in immune tolerance and autoimmune disease development and some metabolic effects from protecting problems leading illnesses.
We must indicate the studies; The Human Microbiome Project (HMP) was a United States National Institutes of Health initiative one, The Earth Microbiome Project (EMP) is an resourcefulness to collect natural samples and analyze the microbial community around the globe, and The Brazilian Microbiome Project (BMP).

Lactobacillus

Wikipedia

- Group I Facultative anaerobic
- Facultatively heterofermentative (group II) including: *L. casei*, *L. curvatus*, *L. plantarum*, *L. sakei*
- Obligately heterofermentative (group III) including: *L. brevis*, *L. buchneri*, *L. fermentum*, *L. reuteri*

Lactobacillus mostly called as Lactic acid bacteria group, thus, they are facultative anaerobic or microaerophilic Gram positive bacteria, non-spore forming ones. Significant component of the microbiota, even at the vaginal flora. This genus convert fructose and other sugars to lactic acid as milk sugar, lactose.
Lactobacillus acidophilus, acid loving milk bacillus, can multiply at rather low pH values (below pH 5.0, as at skin pH) and optimum growth around 37°C. Mostly found at mouth and gastro-intestinal flora. This bacteria is a preferred microbiota for yogurt production as with; *Streptococcus thermophilus* and *Lactobacillus delbrueckii subsp. bulgaricus*.
Lactobacillus delbrueckii is a species of microbiota at the lower reproductive tract of women.
Lactobacillus helveticus is the bacteria of American Swiss and Emmental cheese. Also, making the Cheddar, Parmesan, Romano, Provolone, Mozzarella chesses. The carbon dioxide because of fermentation is the holes/eyes of these Swiss Cheese.
Lactobacillus salivarius is also a probiota at the gastro-intestinal tract, mostly known as the effect of suppression of pathogenic bacteria.

Some *Lactobacillus* species are used as starter cultures in industry for controlled fermentation in the production of yogurt, cheese, sauerkraut, pickles, beer, cider, kimchi, cocoa, kefir, and other fermented foods, as well as animal feeds.

Evidence on Health

- *L. acidophilus* and also, *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus jensenii*, and *Lactobacillus iners* are vaginal flora microorganisms and also at yogurt enriched for the treatment of some vaginal infections; effectiveness for other conditions ranges from unclear to fair negative evidence, thus, effectiveness for other conditions are unclear to negative evidences.
  Thus, the floral arrangement, is not enough for treatment, this is a conditional aspect, not to be cultivated for other microorganisms, like Candida, as producing lactic acid, lowering the pH and others cannot be cultivated. This aspect is biological reality, not to be considered as treatment, not have a strong adherence to mucosa, but just as a not allowed for other microbes to be there.
- *L. acidophilus* may be decreased the incidence of pediatric diarrhea.
  This is an establishing a floral changing and not allowed the others to be grown and protecting from secondary lactose intolerance, and the epithelial protection from the inflammation.
- *L. acidophilus* led to a significant decrease in levels of toxic amines in the blood of dialysis patients with small bowel bacterial overgrowth.
  This is a physiological controlling of the products, that can be harmful.
- At adequate daily feeding levels, *L. acidophilus* may facilitate lactose digestion in lactose-intolerant subjects, mostly common at the Asia and American Indians.
- Powdered milk fermented with *L. helveticus* have been demonstrating, decrease blood pressure, as ACE inhibitory tripeptides, and contradictory studies is also mentioned.
- *Lactobacillus salivarius* has been found to be of benefit in of flatulence, at irritable bowel syndrome. Combinations of the probiotics are most be helpful.
- *Lactobacillus salivarius* has been found to have a wide spectrum of coverage against pathogenic organisms that translocate from the gastrointestinal tract thereby demonstrating therapeutic benefit in the management of pancreatic necrosis. Other probiotic species (*Bifidobacterium bifidum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Lactococcus lactis*) suppressed pro-inflammatory cytokines and further suppressed bacterial overgrowth in the small intestine leading to a reduction in bacterial translocation..
- Atopic dermatitis symptoms have been shown to be reversed in some children.
- They are, the probiotics are generally safe. Passage of viable bacteria to blood, may cause in theoretically sepsis. Like preterm infants the defensive of immune systems are lowered and may risk for adverse event, thus, the Lactobacillus can hardly be cultivated at tissues, they are facultative anaerobic, tissue condition is aerobic and high pH 7.35, according to 5.0. Clinically not a real case is confirmed, all are theoretical estimation.
- Lactobacillus and Bifidobacterial probiotics can reduce clinical symptoms of pouchitis and cholangitis.

- *L. acidophilus* is used to prevent necrotizing enterocolitis and other neonatal infections.
- *Lactobacillus* species produce hydrogen peroxide, inhibits and may be lethal to pathogens, like *Candida albicans*.
- The antibacterial and antifungal activity of *Lactobacillus* species rely on production of bacteriocin and low molecular weight compounds that inhibits these microorganisms.
- *Lactobacilli* characteristically cause existing carious lesions to progress, especially those in coronal caries. Thus, some evidences encountered, for oral health *Lactobacillus* have in relation.
- Research continues into the role of *Lactobacillus* species and the possible role it has in emotional and mental health.
- Lactobacilli, especially *L. casei* and *L. brevis*, are beer spoilage organisms, as; Belgian lambics and American wild ales with a tart flavor.

Vitreoscilla

Wikipedia

Vitreoscilla is a genus of Gram-negative aerobic bacterium; biological and biotechnological applications are encountered.

Evidence on Health

- ***Vitreoscilla*** is submissions including promotion of cell growth, protein synthesis, metabolic productivity, enhanced metabolism, nitric oxide detoxification, respiration, cellular detoxification, fermentation, biodegradation, production of ethanol etc.

Bifidobacterium

Wikipedia

Bifidobacterium is a Gram positive, anaerobic bacteria, mostly at the gastrointestinal tract, mostly they are colon flora, and at vagina. Before is named as; "*Lactobacillus bifidus*".

Bifidobacterium is cultured at different oxygen concentrations as;

- Oxygen hypersensitive
- Oxygen sensitive
- Oxygen tolerant
- Microaerophilic

The primary factor responsible for aerobic growth inhibition is for production of hydrogen peroxide at highly aerated conditions.

Evidence on Health

- *Bifidobacterium* species administered as a probiotic have been found be an effective treatment for some types of inflammatory bowel disease and have no negative side effects. *Bifidobacterium animalis* bacteria found in a sample of Activia yogurt.
- ***Bifidobacterium longum*** is micro-aerotolerant anaerobe, thus, early colonized at infants, thus, represents up to 90% of the bacteria of an infant's gastrointestinal tract. They prevent growth of pathogenic organisms. *B. longum* is non-pathogenic and is often added to food products.

- ***Bifidobacterium*** possess strong electrostatic charges that aid in the adhesion of *B. longum* to intestinal endothelial cells.
- ***B. longum*** in action of hydrolases, deaminases, and dehydratases to ferment amino acids. ***B. longum*** also has bile salt hydrolases to hydrolyze bile salts into amino acids and bile acids, may be act better tolerable to bile salts
- ***B. longum*** may be used in combination with conventional therapies to treating ulcerative colitis.
- ***B. longum*** was shown to shorten the duration and minimize the severity of symptoms associated with common cold for influenza, similar effect as neuraminidase inhibitors.

Bifidobacterium animalis subsp. lactis

Bifidobacterium animalis can be found in the large intestines of most mammals/humans.

Evidence on Health

Bifidobacterium animalis subspecies lactis administered in combination with other probiotics has showed a small beneficial effect with ulcerative colitis.

Streptococcus thermophilus

Streptococcus thermophilus also known as ***Streptococcus salivarius* subsp. *Thermophilus*** is also classified as a lactic acid bacterium. ***Streptococcus thermophilus*** is ability to thrive at high temperatures, and mozzarella cheese is a product of this microbiomes.
Streptococcus thermophilus is differs; food industries consider *S. thermophilus* a safer bacterium than many other *Streptococcus* species as; *S. pneumoniae* and *S. pyogenes.*
S. thermophilus produced low moisture cheese and decreased the bitterness of cheese. It had been concluded that applying both *L. lactis* and *S. thermophilus* strains create higher quality reduced-fat cheese with similar characteristics to regular cheese.

Evidence on Health

- Live cultures of *S. thermophilus* make it easier for people who are lactose intolerant to digest dairy products.
- Chemotherapy caused mucositis, severe inflammation on small intestines. The intestinal tissues in those pretreated with streptococcus thermophilus, thus, functioned more healthily and were less distressed.
- In mice lung cancer incidence is one third reduced by eating *L. d. bulgaricus* was fed mice.
- Strains of *S. thermophilus* have also reduced risks of AAD (antibiotic-associated diarrhea).

Lactobacillus delbrueckii subsp. bulgaricus

Lactobacillus delbrueckii* subsp. *bulgaricus is used for the production of yogurt and other fermented foods, thus, by *Streptococcus thermophilus* they gives yogurt its tart flavor and acts as a preservative. *L bulgaricus* have been shown to kill undesired bacteria *in vitro*, by producing bacteriocin's.

Evidence on Health

- Proteolytic bacteria such as *Clostridia*, that is a part of the normal intestinal flora, produce toxic substances including phenols, ammonia, indoles and digestive proteins/enzymes, caused auto digestion of the intestine, leading necrosis and septic shock. Lactic acid bacteria because of low pH, inhibits their growth.

Lactobacillus salivarius

Lactobacillus salivarius is a microbiota, commonly considered as suppression of pathogenic bacteria.

Evidence on Health

- Irritable bowel syndrome
- Pancreatic necrosis
- Atopic Dermatitis

Comment

In Wikipedia, the comment is indicated as below;

1) The manipulation of the gut flora is complex and may cause bacteria-host interactions.[12]
2) Although probiotics, in general, are considered safe, there are concerns about their use in certain cases.[12][13]
3) Some people, such as those with compromised immune systems, short bowel syndrome, central venous catheters, heart valve disease and premature infants, may be at higher risk for adverse events.[14]
4) Rarely, consumption of probiotics may cause bacteremia, and sepsis, potentially fatal infections in children with lowered immune systems or who are already critically ill.[15]

The indicating literatures are discussed below

1. **May cause bacteria host reactions**

   12: *Durchschein F, Petritsch W, Hammer HF (2016). "Diet therapy for inflammatory bowel diseases: The established and the new.". World J Gastroenterol (Review). 22 (7): 2179–94.*

   - *"The scientific literature shows that dietary factors might influence the risk of developing IBD, that dysbiosis induced by nutrition contributes to the pathogenesis of IBD, and that diet may serve as a symptomatic treatment for irritable bowel syndrome-like symptoms in IBD."*

     Comment: For making immune reactions, the microbes or the reactions have a confrontation any inflammatory response as indicated above. Any tissue reaction, infiltration NO, any antibody Establishing NO, may be bacteremia but not sepsis confrontations, so this indication is only a suspicious one but not clinically and evidenced based confrontation.

   - *"The use of specific probiotics in patients with IBD (*inflammatory bowel diseases*) can be recommended only in special clinical situations. There is no evidence for efficacy of*

*probiotics in CD (*Crohn's disease*). By contrast, studies in UC (*ulcerative colitis*) have shown a beneficial effect in selected patients."*

Comment: The Establishing gastro-intestinal physiological flora is not mentioned as a treatment application, this is only a reconstruction the Physiology form the Pathological conditions, the flora. This is not a medical efficacy, this is confrontation of the Physiology, thus, a kind of Protection from pathogenic flora. Especially some makes tissue necrosis and destruction of cells.

- "*For patients with pouchitis, antibiotic treatment followed by probiotics, like VSL#3 or Lactobacillus GG, is effective. When probiotics are used, the risk of bacterial translocation and subsequent bacteremia should be considered. More understanding of the normal intestinal microflora, and better characterization of probiotic strains at the phenotypic and genomic levels is needed as well as clarification of the mechanisms of action in different clinical settings."*

  Comment: In diarrhea, the intestinal structure is destroyed, even all the mucosa is thorn up, so bacteremia can be easily noticed and infection can be noticed. The secondary lactose intolerance and the pathogenic microbes as Salmonella be stay there and be a porter of it, even clinically be normal. So, who will be cleaning this pathogenic flora, be physiologic ones? Probiotics be indicated as the only one, not the antibiotics. So, at 8-12 hours' probiotics will be Cover the intestines and control the pathogenic flora.

  The microbiota at the blood cannot be harmful, thus, cannot be on oxidative state, not making tissue and cell degeneration, tissue necrosis, confirm lactic Acidosis that will be metabolized by the body. Not forming abscess and other side effects. Not any immune response, but T cell action will be benefit of the host.
- "*The exact pathomechanism of IBD is remains unexplained*"

  Comment: Physiological pathology is not known, how can be probiotics be treat or helpful. This is only to confirm the physiological intestinal flora, not be harmful, in compared the Pathological ones.
- "*As dietary antigens, along with bacterial antigens are the most common types of luminal antigen, it is reasonable to suppose that dietary factors may play an important role in the pathogenesis of IBD, possibly by interacting with gut microbiota and the mucosal immune system*."

  Comment: If the pathogenesis is in estimation for the dietary factors, then the physiological flora will be provoked as normal flora, may be a suggestion of this healing.
- *"…microbiota provide the most common luminal antigens in the bowel, and these could influence intestinal inflammation. The human colonic microbiota plays a central role in inducing disorders of immune function and inflammation and studies in recent decades have shown that bacteria are involved in the pathogenesis of IBD. Alterations in the gut microbiome have been associated with IBD. Ewaschuk et al found that Bacteroides spp., Enterococcis faecalis, Enterobacter cloacae, intestinal Heliobacter spp., Fusobacterium spp., adherent/invasive Escherichia coli strains, Eubacterium and Peptostreptococcus spp. seem to be harmful intestinal microbesIn contrast, Lactobacillus spp., Bifidobacterium*

spp., Streptococcus salivarius, Saccharomyces boulardii (S. boulardii), Clostridium butyricum, Ruminococci and Escherichia coli (E. coli) Nissle 1917 seem to be beneficial".

Comment: If something seems to be beneficial, why not used? The point is not giving or performing other than physiology, just making, reestablishing the normal, the physiological flora.

- "*Potential mechanisms: The mechanism by which EN improves CD is unclear. Hypotheses include altered or reduced gut microbiota, avoidance of long-chain fat, which impairs macrophage function, and avoidance of other harmful components of normal food, like emulsifiers or nano-particles as additives*."

  Comment: Reducing of microbiomes are considered as a causative factor.

- "*A study with paediatric CD patients looked at the impact of exclusive EN on gut microbiota, which showed reduced diversity and an increase in Protobacteria. Leach et al compared the bacteria in the stool in patients with CD under exclusive enteral nutrition to a group of healthy controls under a regular diet. At the start of the study, the diversity of bacteria in the two groups was similar but after 8 wk., the patients treated with exclusive EN had significantly less bacterial diversity than the control group."*

  Comment: Thus, physiological microflora establishing is the aim for the natural confirmation.

- *"There is growing evidence for an association between IBD and an alteration in the gut microbiota but due to the complexity of the gut microbiota, research on this is still in its early stages. Studies have shown a disbalance in the gut between protective vs harmful intestinal bacteria with, e.g., an increase in mucosa-associated Escherichia coli and a reduction in bifidobacterium and lactobacillus species. Strategies modulating this dysbiosis might be a therapeutic option in IBD. Antibacterial treatment has been used, but with limited effect. Probiotics may improve intestinal microbial balance, enhancing gut barrier function and improving local immune response. Probiotics are live microorganisms, which when administered in adequate amounts, confer a health benefit on the host. Their effects are strain specific, so that comparisons and meta-analyses of studies using different probiotics are problematic."*

  Comment: The indication of "*Probiotics may improve intestinal microbial balance, enhancing gut barrier function and improving local immune response*" is true or wrong, but the physiology establishing is naturally important and essential.

- *"Bacteria associated with probiotic activity like lactobacilli or bifidobacteria have been used as well as non-bacterial organisms such as S. boulardii, but it is a challenge to manipulate the highly individual gut microbiota. Potential mechanisms of probiotics are competitive interactions with the gut microbiota, production of antimicrobial metabolites, and interaction with the epithelium or immune modulation. Cells involved in both the innate and adaptive immune responses, like B cells, T cells and dendritic cells as well as macrophages, might be affected. Probiotic bacteria are able to antagonize pathogenic bacteria by reducing luminal pH and inhibiting bacterial adherence and translocation; they can also produce antibacterial substances and defensins. For example, invasion of an epithelial cell line by invasive E. coli isolated from patients with CD was prevented by pre- or co-incubation with E. coli Nissle 1917. Pre-treatment of IL-10 deficient mice with Lactobacillus reuteri and L. casei can reduce Heliobacter hepaticus-induced colitis. A decrease in mucosal secretion of inflammatory cytokines was shown to be induced by E. coli (Nissle 1917) in models of experimental colitis. Probiotics also influence cell-cell interactions and stability through modulation of intestinal barrier function. Alterations in*

mucus, chloride secretion or changes in tight junction protein expression by epithelial cells might be mechanisms for improved gut mucosal barrier function. There are no human data showing any effect of probiotics on dysplasia or colon cancer; however, in animal studies probiotics also seem to reduce the progression from inflammation to dysplasia and finally to colon cancer. Oral administration of Lactobacillus salivarius UCC118 was shown to reduce the incidence of colon cancer as well as the severity of mucosal inflammation in IL-10-/- mice vs placebo. Oral administration may not be required for certain probiotic effects: Il-10-/- mice had fewer proinflammatory cytokines after subcutaneous injection of L. salivarius UCC18. Consequently, probiotics might improve IBD by regulating the inflammatory response or modulating gut microbiota composition. Many studies have tried to determine the effect of various probiotics in IBD.

Comment: The immune positive effects are indicated above section at the Literature.

- *"The only positive study, by Guslandi et al, found that the yeast S. boulardii had an effect in CD… There are data that suggest that certain strains of probiotics are effective in the management of UC… The ECCO guidelines recommend probiotics as a therapeutic option for maintaining antibiotic-induced remission in recurrent pouchitis in pediatric UC"*

  Comment: This will not be considered as treatment, or vice versa. Just a physiological reconstruction of the intestinal flora.
- *"This probiotic bacterium develops antagonistic activity against enterobacteria such as Salmonella enteritidis, Shigella dysenteriae, Yersinia enterocolitica and Vibrio cholera".*

  Comment: This is the main function of the intestinal flora, not to be allowed growth and cultivated.

Result

The result is indicated as Table 1: Thus, the microbiota cannot be considered as the treatment, it is just an establishing the natural flora, better than the pathological one. Primum non nocere ethical consideration, it is a choice of than harmful one. Benefit at Pouchitis is a good indication to be helpful

Table 11/1: The effect of Probiotics at CD and UC.

	Crohn's disease			Ulcerative colitis			
	Induce remission	Maintain remission	Postop.	Induce remission	Maintain remission	Postop.	Pouchitis
Probiotics	No effect	No effect	No effect	+	+	Not tested	++

2. **Although probiotics, in general, are considered safe, there are concerns about their use in certain cases**

   13: Boyle RJ, Robins-Browne RM, Tang ML (2006). "Probiotic use in clinical practice: what are the risks?". Am J Clin Nutr (Review). 83 (6): 1256–64; quiz 1446–7.

   - Abstract: *"Probiotics have been advocated for the prevention and treatment of a wide range of diseases, and there is strong evidence for their efficacy in some clinical scenarios.*

Probiotics are now widely used in many countries by consumers and in clinical practice. Given the increasingly widespread use of probiotics, a thorough understanding of their risks and benefits is imperative. In this article, we review the safety of probiotics and discuss areas of uncertainty regarding their use. Although probiotics have an excellent overall safety record, they should be used with caution in certain patient groups—particularly neonates born prematurely or with immune deficiency. Because of the paucity of information regarding the mechanisms through which probiotics act, appropriate administrative regimens, and probiotic interactions, further investigation is needed in these areas. Finally, note that the properties of different probiotic species vary and can be strain-specific. Therefore, the effects of one probiotic strain should not be generalized to others without confirmation in separate studies. Careful consideration should be given to these issues before patients are advised to use probiotic supplements in clinical practice."

Comment: Especially the immune deficient patients, the pathogenic flora confirms several adverse symptoms, even sepsis and hard to be treated, especially *Klebsiella spp* and gram negative microorganisms and *Candida spp*. Therefore, the physiological flora establishing is essential, not for the treatment, but protection from the pathologic ones. Intestine cannot be sterilized and cannot be controlled the bacterium and fungi therefore be confirmation of physiological ones is essential. It is not a treatment, just establishing a physiological flora.

- *"The strongest evidence for the use of probiotics is in the management of diarrheal diseases. For example, a meta-analysis of randomized controlled trials has shown that many probiotics are effective in preventing antibiotic-associated diarrhea, including the yeast Saccharomyces boulardii and the bacterium Lactobacillus acidophilus in combination with L. bulgaricus, L. rhamnosus strain GG [American Type Culture Collection (ATCC) 53103; LGG], and Enterococcus faecium strain SF68. A separate meta-analysis of randomized controlled trials has shown a variety of probiotics (including Lactobacillus species, Enterococcus species, and S. boulardii) to be effective in the treatment of infective diarrhea in both adults and children. In this analysis, probiotics were found to reduce the mean duration of diarrhea by >30 h.*
- *There is also support from randomized controlled trials for the efficacy of a probiotic mix (containing 3 × 10^{11} CFU L. bulgaricus, L. casei, L. plantarum, L. acidophilus, Bifidobacterium longum, B. breve, B. infantis, and S. thermophilus) in preventing flares of chronic pouchitis in patients with inflammatory bowel disease and for the use of a different probiotic mix [B. lactis Bb12 and Lactobacillus reuteri (ATCC 55730) at 1 × 10^{7} CFU/g in a cow milk formula] to prevent diarrheal illness in infants attending childcare.*
- *Probiotic therapy has also been explored in non-gastrointestinal diseases, including the treatment and prevention of atopic eczema. Nevertheless, the evidence to date suggests that the major clinical effects of probiotics are seen in gastrointestinal disorders."*.

  Comment: For diarrheal disease, commonly antibiotic associated ones, the symptom is reduced significantly. The other indications are the intestinal flora reconstruction.
- "… are classified as biological products", "Therapeutic Goods Administration and are usually regulated as complementary medicines", "probiotic strains are widely regarded as safe"

  Comment: Food and Drug Administration requirements are indicated as above concept. These probiotics are rarely concern as drug in medicine, regarding as physiological concept.

- *"Many small studies also support the safety of particular probiotic strains in particular high-risk populations. For example, different Lactobacillus strains have been fed to adults and children infected with HIV, to term infants, and to premature infants with no significant adverse effects"* and *"Despite this increased use, no significant increase in Lactobacillus bacteremia or bacteremia attributable to probiotic strains has been observed in southern Finland. Thus, there is a body of evidence that supports the safety of some probiotics, particularly Lactobacillus strains."*

  Comment: Thus, this will not be confirming it as a medicine application, it is indicating that, the physiological intestinal flora is better than the pathogenic one.
- *"One theoretical concern with the safety of probiotics is that some have been designed or chosen to have good adherence to the intestinal mucosa, and this is considered important for their mechanism of action. Adherence to the intestinal mucosa may also increase bacterial translocation and virulence. The most potent probiotics, therefore, may have increased pathogenicity. The relation between mucosal adhesion and pathogenicity in Lactobacillus spp. is supported by the finding that blood culture isolates of Lactobacillus spp. adhere to intestinal mucus in greater numbers than do isolates from human feces or dairy products". "… Many Lactobacillus strains are naturally resistant to vancomycin, which raises concerns regarding the possible transfer of such resistance to more pathogenic organisms, particularly enterococci and Staphylococcus aureus. However, the vancomycin-resistant genes of Lactobacillus spp. are chromosomal and, therefore, not readily transferable to other species. Conjugation studies have not found the vancomycin-resistant genes of lactobacilli to be transferable to other genera."*

  Comment: This is a hypothetical estimation and a warning concept. Thus, the translocation of the resistance and virulence is also demonstrated at the other pathogens and commonly the confrontation of the resistance factor. The microbiota and the other pathogens cannot be get together, the environment of the culture media is differing. One can survive, the other will not be alive.
- *Murine experiments have also shown the potential for probiotics to cause sepsis. For example, Wagner et al colonized athymic mice with human isolates of L. reuteri, L. acidophilus, Bifidobacterium animalis, or LGG. Although athymic adult mice were not adversely affected by the probiotics, colonization with the probiotics L. reuteri and LGG did lead to death in some athymic neonatal mice. This finding suggests that the presence of immune deficiency in neonates may put them at particularly high risk of probiotic sepsis. These theoretical concerns are highlighted by recent case reports of probiotic sepsis in humans.*

  Comment: This is a probability condition, but the pathogenic flora versus the microbiota. *"Most cases of probiotic sepsis have resolved with appropriate antimicrobial therapy, but in some cases patients have developed septic shock. In other cases, the outcome has been fatal, but these fatalities were usually related to underlying disease rather than directly to probiotic sepsis." "… We suggest that the presence of a single major risk factor or more than one minor risk factor merits caution in using probiotics.*
- ***Conclusions**: Probiotics are increasingly being used by consumers for their health benefits and are advocated by many health care professionals. The evidence base for their use in specific clinical scenarios is strong, but they are commonly used in a much wider range of scenarios in which their efficacy is not well established. Herein we reviewed the safety of*

probiotics and highlighted deficiencies in our understanding of their appropriate administration and their mechanisms of action. We found that probiotics are safe for use in otherwise healthy persons, but should be used with caution in some persons because of the risk of sepsis. Newly developed probiotic strains should be thoroughly evaluated for safety before being marketed. Although much remains to be learned regarding the mechanisms of action and the appropriate administration of probiotic strains, it is clear that different strains can have very specific effects. Moreover, their effects may vary in health and disease, in different disease states, and in different age groups. Thus, clinical trial results from one probiotic strain in one population cannot be automatically generalized to other strains or to different populations. Further studies are needed to explore mechanistic issues and probiotic interactions. In view of the increasing use of probiotics as health supplements and therapeutic agents, clinicians need to be aware of the risks and benefits of these treatments.

Comment: This is a medical perspective, nothing is completely being benefit and not any harm, all concerns to unique individual conditions, as preterm infant, according their gestational age etc. As Evidence/Science Based Medicine, nothing is completely true or righteous, everything is continuously being evaluated.

Table 11/2: Causes of bacterial sepsis temporally related to probiotic use in humans

Study	Risk factors	Method of identification[2]	Form of sepsis
Rautio et al	Diabetes mellitus	API 50 CH, PFGE of DNA restriction fragments	Liver abscess
Mackay et al	Mitral regurgitation, dental extraction	API 50 CH, pyrolysis mass spectrometry	Endocarditis
Kunz et al	Prematurity, short-gut syndrome	No confirmatory typing	Bacteremia
	Prematurity, inflamed intestine, short-gut syndrome	PFGE of DNA restriction fragments	Bacteremia
De Groote et al	Prematurity, gastrostomy, short-gut syndrome, CVC, parenteral nutrition, rotavirus diarrhea	rRNA sequencing	Bacteremia
Land et al	Cardiac surgery, antibiotic diarrhea	Repetitive element sequence-based PCR DNA fingerprinting	Endocarditis
	Cerebral palsy, jejunostomy feeding, CVC, antibiotic-associated diarrhea	Repetitive element sequence-based PCR DNA fingerprinting	Bacteremia
Richard et al	Not stated	Antibiotic susceptibility	Bacteremia
	Not stated	Antibiotic susceptibility	Bacteremia
	Neoplastic disease	Antibiotic susceptibility	Bacteremia
	Not stated	Antibiotic susceptibility	Bacteremia
Oggioni et al	Chronic lymphocytic leukemia	16S rRNA sequencing	Bacteremia

Table 11/3: Proposed risk factors for probiotic sepsis

Major risk factors

1) Immune compromise, including a debilitated state or malignancy
2) Premature infants

Minor risk factors

1) CVC
2) Impaired intestinal epithelial barrier, e.g., diarrheal illness, intestinal inflammation
3) Administration of probiotic by jejunostomy
4) Concomitant administration of broad spectrum antibiotics to which probiotic is resistant
5) Probiotics with properties of high mucosal adhesion or known pathogenicity
6) Cardiac valvular disease (*Lactobacillus* probiotics only)

Result

The result is indicated there is a susceptibility, but for pathogenic flora this risk is more obvious.

3. **Some people, such as those with** compromised immune systems**,** short bowel syndrome**,** central venous catheters**,** heart valve disease **and** premature infants**, may be at higher risk for adverse events.**[14]
   14: Doron S, Snydman DR (2015). "Risk and safety of probiotics."***. Clin Infect Dis (Review). 60 Suppl 2: S129–34.***
   - "*Abstract: Probiotics have been used safely for years. Safety outcomes are inconsistently reported in published clinical trials. In 2011, a report released by the Agency for Healthcare Research and Quality concluded that, although the existing probiotic clinical trials reveal no evidence of increased risk, "the current literature is not well equipped to answer questions on the safety of probiotics in intervention studies with confidence." Critics point out that the preponderance of evidence, including the long history of safe probiotic use as well as data from clinical trials, and animal and in vitro studies all support the assumption that probiotics are generally safe for most populations. Theoretical risks have been described in case reports, clinical trial results and experimental models, include systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gene transfer and gastrointestinal side effects. More research is needed to properly describe the incidence and severity of adverse events related to probiotics.*"
     Comment: These findings are due to the condition of the case; immune reaction of the individual, preterm infants or direct the microbiota acts. Mostly accepted as the individual reaction, microbiota is better than pathogenic intestinal flora.
   - ***"Implications for Future Research****: … efficacy of probiotics, at the time of this writing, only 7 US federally funded human interventional studies are being conducted in this field (http://projectreporter.nih.gov/reporter_SearchResults; accessed 12 February 2015).*
     Comment: Further governmental studies are concerned for new aspects.

4. **Rarely, consumption of probiotics may cause** bacteremia**, and** sepsis**, potentially fatal infections in children with lowered immune systems or who are already critically ill.**[15]
   15: Jump up ***Singhi SC, Kumar S (2016).*** "Probiotics in critically ill children."***. F1000Res (Review). 5.***
   - "***Abstract****: Gut microflora contribute greatly to immune and nutritive functions and act as a physical barrier against pathogenic organisms across the gut mucosa. Critical illness disrupts the balance between host and gut microflora, facilitating colonization, overgrowth, and translocation of pathogens and microbial products across intestinal mucosal barrier and causing systemic inflammatory response syndrome and sepsis. Commonly used probiotics, which have been developed from organisms that form gut microbiota, singly or in combination, can restore gut microflora and offer the benefits similar to those offered by normal gut flora, namely immune enhancement, improved barrier function of the gastrointestinal tract (GIT), and prevention of bacterial translocation. Enteral supplementation of probiotic strains containing either Lactobacillus alone or in combination with Bifidobacterium reduced the incidence and severity of*

necrotizing enterocolitis and all-cause mortality in preterm infants. Orally administered Lactobacillus casei subspecies rhamnosus, Lactobacillus reuteri, and Lactobacillus rhamnosus were effective in the prevention of late-onset sepsis and GIT colonization by Candida in preterm very low birth weight infants. In critically ill children, probiotics are effective in the prevention and treatment of antibiotic-associated diarrhea. Oral administration of a mix of probiotics for 1 week to children on broad-spectrum antibiotics in a pediatric intensive care unit decreased GIT colonization by Candida, led to a 50% reduction in candiduria, and showed a trend toward decreased incidence of candidemia. However, routine use of probiotics cannot be supported on the basis of current scientific evidence. Safety of probiotics is also a concern; rarely, probiotics may cause bacteremia, fungemia, and sepsis in immunocompromised critically ill children. More studies are needed to answer questions on the effectiveness of a mix versus single-strain probiotics, optimum dosage regimens and duration of treatment, cost effectiveness, and risk-benefit potential for the prevention and treatment of various critical illnesses."

Comment: This confirms mostly on the positive aspects. The point, microbiota might be noticed as the physiological intestinal flora. Not as treatment as drug, but physiology, the environmental health status for the Human, especially for Newborn babies, preterm infants.

Table 11/4: Beneficial functions performed by gut microbiota.

Beneficial functions	Details of beneficial functions
Immune response	Gut microflora stimulate the proliferation and differentiation of epithelial cells in large and small intestines, modulate innate and adaptive immune response and development of competent gut-associated immune system, and maintain an immunologically balanced inflammatory response
Physical barrier function (colonization resistance)	Gut microbiota provide a physical barrier against pathogen invasion by competing for epithelial cell adhesion sites, preventing epithelial invasion, competing for available nutrients affecting the survival of potential pathogens, and producing anti-bacterial substances (e.g. bacteriocins and lactic acid), making the environment unsuitable for the growth of pathogens
Nutritive functions	Gut microbiota produce several enzymes for fermentation of non-digestible dietary residue and endogenously secreted mucus and help in recovering lost energy in the form of short-chain fatty acids. They also help in the absorption of calcium, magnesium, and iron; synthesis of vitamins (folic acid and vitamin B1, B2, B3, B12, and K); biotransformation of bile acids; and conversion of pro-drugs to active metabolites.

Table 11/5: Experimental studies showing mechanisms of beneficial effects of probiotics.

Mechanism of action	Authors	Experimental group	Outcome
Probiotics maintain healthy flora and reduce the growth of pathogens and colonization.	Jiang et al.	Opportunistic oral Candida albicans	L. rhamnosus GG had inhibitory activity against Candida glabrata. None had inhibitory activity against Candida krusei.
	Machairas et al.	Experimental infection resistant Pseudomonas	L. plantarum pretreatment significantly increased survival after challenge by either P. aeruginosa (66.7% versus 31.3%; P = 0.026) or E. coli (56% versus 12%, P = 0.003).

Mechanism of action	Authors	Experimental group	Outcome
		aeruginosa and Escherichia coli	
Probiotics prevent bacterial translocation.	Mangell et al.	Endotoxemia rat model	L. plantarum 299v pretreatment reduced bacterial translocation to 0% and 12% in mesenteric lymph nodes and liver, respectively.
	Ruan et al.	In hemorrhagic-shock rat model	Pretreatment with encapsulated Bifidobacteria reduced incidence of bacterial translocation to mesenteric lymph nodes compared with PBS (40% versus 80%, P <0.05). Non-significant reduction in bacterial translocation by intact Bifidobacteria when compared with PBS control (55% versus 80%, P >0.05).
	Sánchez et al.	In rats with carbon tetrachloride-induced cirrhosis	Decreased incidence of bacterial translocation in VSL#3 group than in water group (8% versus 50%; P = 0.03)

Table 11/6: Clinical studies showing mechanisms of beneficial effects of probiotics.

Mechanism of action	Authors	Patient group	Outcome
Probiotics maintain healthy flora and reduce the growth of pathogens and colonization.	Shimizu et al.	Randomized controlled trial (RCT) involving patients with systemic inflammatory response syndrome (SIRS) (n = 29)	Probiotic group had significantly greater levels of beneficial Bifidobacterium, Lactobacillus, and organic acids in the gut. The incidences of infectious complications were significantly lower in the probiotic group (enteritis 7% versus 46%; pneumonia 20% versus 52%; bacteremia 10% versus 33%).
	Hayakawa et al.	RCT involving mechanically ventilated patients (n = 47)	Synbiotic group had significantly increased Bifidobacterium and Lactobacillus (to 100 times the initial level), increased acetic acid concentration (71.1±15.9 versus 46.8±24.1μmol/g), decreased pH, decreased Gram-negative rod (to one-tenth of the initial level) in the gut, and decreased Pseudomonas aeruginosa in the lower respiratory tract when compared with the control group.
	Jain et al.	RCT involving intensive care unit (ICU) patients (n = 90)	Synbiotic group had lower incidence of potentially pathogenic bacteria (43% versus 75%, P = 0.05) and multiple organisms (39% versus 75%, P = 0.01) in nasogastric aspirates than controls.
	Mohan et al.	RCT including preterm neonates (n = 69)	Probiotic group had higher counts of Bifidobacterium (log10 values per grams of fecal wet weight: 8.18±0.54 versus 4.82±0.51; P = 0.001); and lower counts of Enterobacteriaceae (7.80±0.34 versus 9.03±0.35; P = 0.015) and Clostridium spp. (4.89±0.30 versus 5.99±0.32; P = 0.014) than in placebo group.
	Manzoni et al.	RCT including very low birth weight preterm babies (n = 80)	Reduced incidence of Candida colonization in gut in probiotic group as compared with placebo group (23.1% versus 48.8%; P = 0.01).

Mechanism of action	Authors	Patient group	Outcome
Probiotics reduce inflammation	Sanaie et al.	RCT involving critically ill patients (n = 40)	Reduced inflammation (reduced acute physiology and chronic health evaluation II [APACHE II] score, sequential organ failure assessment [SOFA], interleukin-6 [IL-6], procalcitonin, and protein)
	McNaught et al.	RCT involving critically ill patients (n = 103)	Late attenuating effect (after 15 days) on SIRS (as measured by serum IL-6 levels)
	Ebrahimi-Mameghani et al.	RCT involving ICU cases (n = 40)	Reduction in inflammation (C-reactive protein and APACHE II score). No significant change in markers of oxidative stress: total antioxidant capacity (TAC) and malondialdehyde (MDA) levels.

Probiotic use in critically ill children

- *Studies have evaluated the role of probiotics in critically ill children for the prevention and treatment of necrotizing enterocolitis (NEC),*
- *Antibiotic-associated diarrhea (AAD),*
- *And HCAIs, including ventilator-associated pneumonia (VAP),*
- *Candida colonization, and invasive candidiasis.*

Table 11/7: The effect of probiotics on antibiotic-associated diarrhea.

Authors (year)	Number of trials	Results
D'Souza et al. (2002)	Nine randomized controlled trials (RCTs), including two pediatric RCTs	Probiotics were effective in the prevention of antibiotic-associated diarrhea (AAD) (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.26–0.53, P<0.001). Saccharomyces boulardii and Lactobacilli had the best potential.
Szajewska et al. (2006)	Six pediatric RCTs	Treatment with probiotics compared with placebo reduced the risk of AAD from 28.5% to 11.9% (risk ratio [RR] 0.44, 95% CI 0.25–0.77).
Johnston et al. (2006)	Six pediatric RCTs	Probiotics resulted in significant reduction in the incidence of AAD (RR 0.43, 95% CI 0.25–0.75).
Hempel et al. (2012)	63 RCTs, all ages	Probiotics associated with significant reduction in AAD (RR 0.58, 95% CI 0.50–0.68, P<0.001).
Szajewska et al. (2015)	21 RCTs involving children and adults	S. boulardii compared with placebo or no treatment reduced risk of AAD from 18.7% to 8.5% (RR 0.47, 95% CI 0.38–0.57). In children, from 20.9% to 8.8% (six RCTs, n = 1653, RR 0.43, 95% CI 0.3–0.6). In adults, from 17.4% to 8.2% (15 RCTs, n = 3114, RR 0.49, 95% CI 0.38–0.63).
Szajewska et al. (2015)	12 RCTs involving children and adults	Lactobacillus rhamnosus GG compared with placebo or no additional treatment reduced risk of AAD from 22.4% to 12.3% (RR 0.49, 95% CI 0.29–0.83).

Safety of probiotics

Although most commercially available probiotic strains are widely regarded as safe, there are some concerns with respect to safety, particularly in severely debilitated or immunosuppressed patients. Though

- *Probiotics have the ability to restore the imbalance of intestinal microbiota and function in critically ill children and have been used for various indications, including the prevention of AAD, HCAIs, VAP, Candida colonization, and invasive candidiasis. Safety may be of concern in critically ill, fragile children, as probiotic strains may (albeit rarely) cause bacteremia, fungemia, and sepsis. Well-designed multi-center RCTs are needed to address these issues before the routine use of probiotics is recommended in critically ill children.*
- *L. rhamnosus belongs to the normal human rectal, oral, and vaginal mucosal flora, there are a few case reports of liver abscess due to L. rhamnosus, lactobacillemia, and infective endocarditis.*
    - *Recently, there have been case reports of B. longum bacteremia in preterm infants receiving probiotics.*
    - *Kunz et al. described two premature infants with short gut syndrome who were fed via gastrostomy or jejunostomy and developed Lactobacillus bacteremia while taking Lactobacillus GG supplements.*
    - *Nonetheless, the risk of infection due to Lactobacilli is extremely rare and is estimated to cause 0.05 to 0.4% of cases of infective endocarditis and bacteremia.*

Last Verdict

1) Microbiota is a physiological intestinal flora, serve, protect and be established them is essential basic medical practice.
2) Primum non nocere, is the ethical principles, intestinal flora is essential, cannot be sterilized, so, some bacteria are concern. The choice whether pathological or microbiota. Which one you prefer; microbiota versus pathologic flora?
3) To be positive effect is an assumption, if will be in pleased, if not better than the other ones, pathological flora.

The giving, supporting and be on the microbiota has been several reasoning but, the best one to be establishing physiological flora, with mother's milk.