



REVIEW PAPER

A potential usage of probiotics in prevention and treatment of neutropenic enterocolitis

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ABSTRACT

Introduction and aim. Neutropenic enterocolitis is a severe disease that affects patients with immunodeficiency and is often related with the chemotherapy of the hematologic malignancies. Its pathophysiology is not fully understood. Neutropenic colitis may lead to sepsis, gastrointestinal bleeding and even perforations requiring surgical management. The therapy consists of antibiotic therapy, transfusions, hematopoietic growth factor treatment, usage of fluids and electrolytes, bowel rest and even surgical operations. The aim of this review is to consider the potential usage of probiotics in the prevention and treatment of neutropenic enterocolitis.

Material and methods. References for that article were found through PubMed and Google Scholar, using terms: "neutropenic enterocolitis" and "probiotics"; or "gut microbiota" and "neutropenic enterocolitis". The research was limited to abstracts and available full-text articles.

Analysis of the literature. The most possible mechanism of neutropenic enterocolitis development appoints bacterial invasion with co-existing immunodeficiency. The probiotics appeal as beneficial agents in both prevention and treatment of neutropenic enterocolitis in according to their impact on gut immune barrier improvement. However older societies' guidelines were cautious, the most modern ones appoint probiotics as a promising agent in neutropenic enterocolitis, what corresponds with results from current randomized clinical trials.

Conclusion. As neutropenic enterocolitis is a severe disease we need to look for better or alternative therapies of that state. The probiotics seems to have beneficial effects in terms of prevention and treatment of neutropenic enterocolitis due to their impact on gut immune barrier. Benefits of such therapy are reflected in current societies' guidelines which consider probiotics as a promising agent in neutropenic enterocolitis.

Keywords. oncology, neutropenic enterocolitis, probiotics

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Introduction

Neutropenic enterocolitis (NE) is a severe disease that affects patients with immunodeficiency and is often related with the chemotherapy.^{1,2} However usually NE is associated with hematological malignances, it may also occur in according to solid tumors therapy.³ Usually it affects terminal ileum and right colon.⁴

Its pathophysiology is not fully understood. Damaged intestinal mucosa combined with neutropenia (neutrophil count < 500/μL increases the risk) and immunodeficiency leads to interstitial edema, engorged vessel, vascular congestions and bacterial, fungal or viral invasion (predominantly *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus cereus*, *Klebsiella* spp., *Enterococci*, *Clostridium* spp., and *Candida* spp.).⁵⁻⁷ That mucosal damage may result from the usage of chemotherapeutics with gastrointestinal toxicity.⁵ Medications that predispose to NE are taxane drugs, cyclophosphamide, vincristine, methotrexate, cytarabine, daunorubicin, fludarabine, doxorubicin, idarubicin, 6-thioguanine, deoxycoformycin, 5-fluorouracil, epirubicin, docetaxel, cyclosporine, arabinoside, gemcitabine, leucovorin.⁸⁻¹⁰

As NE is a rare syndrome and has a nonspecific presentation it may resemble other diseases.⁵ That diagnosis may be indicated by concomitance of symptoms such as neutropenia, abdominal pain, diarrhea, nausea and vomiting, fever and thickening of bowel wall seen in radiological examination.⁵⁻⁷

NE may lead to sepsis (predominantly *C. septicum*, *Citrobacter freundii*, *Stomatococcus mucilaginosus*, and *Stenotrophomonas maltophilia*), gastrointestinal bleeding and even perforations requiring surgery.^{6,11} Estimated mortality varies from 23% in intensive care unit patients to 42.2% of those who needed surgical treatment.^{6,12}

There are still discussion about optimal therapy for NE. Currently it consists of antibiotic therapy, transfusions, hematopoietic growth factor treatment and surgical operations.⁶

On the other hand, recent studies focused on gut microbiota condition and its meaning for human health resulted with significant usage of probiotics in diseases like *Helicobacter pylori* infection¹³ or inflammatory bowel disease.¹⁴⁻¹⁶

Aim

The aim of this review is to consider the potential usage of probiotics in the prevention and treatment of NE.

Material and methods

References for that article were found through PubMed and Google Scholar, using terms: “neutropenic enterocolitis” and “probiotics”, or “gut microbiota” and “neutropenic enterocolitis”. The research was limited to abstracts and available full-text articles.

Analysis of the literature

However the pathophysiology of NE remains unclear, the most possible mechanism of its developments is local bacterial invasion of intestine walls, unprotected due to neutropenia and dysbiotic microbiota (both caused by aggressive chemotherapy).⁶ Oncological chemotherapeutics have impact on drug pharmacokinetics, what may result up with gastrointestinal toxicity, making a gate for bacterial invasion.¹⁷ Disorders in gut microbiota appeals as common among hematological patients, even as a result of stem cells transplant.¹⁸

In patients with NE level of dysbiosis correlates with higher degree of disease, on the one hand prolonging the treatment time, but on the other hand – without a significant increase of mortality rate.¹⁹ This dysbiosis may also be iatrogenic – the antibiotic therapy used before the oncological treatment increases the risk of NE development, what may suggest that microbiota impairments are more dangerous for the patient than neutropenia indeed.²⁰ The important factor increasing risk of NE is gut mucositis.⁶ In according to mucositis, the beneficial effect of probiotic intake also is suggested.^{21,22}

The usage of probiotics (particularly *Lactobacillus rhamnosus* GG) significantly reduced the prevalence and severity of gastrointestinal side effects of chemotherapy in patients with acute lymphoblastic leukemia in a prospective cohort study.²³

The first randomized clinical trial on the usage of probiotics in chemotherapy-related diarrhea was published in 2007. The study was concerned on the impact of *Lactobacillus rhamnosus* GG supplementation in patients with 5-fluorouracil therapy. The patients with probiotic had significantly lower prevalence of severe diarrhea (22 vs 37%, $p=0.027$), reported less abdominal discomfort and needed chemotherapy doses reduction less frequently.²⁴ The other research group appointed similar results using *Lactobacillus acidophilus* LA-5 plus *Bifidobacterium animalis* subsp. *lactis* BB-12 in patients with cervical cancer – the research group reported significantly lower occurrence of acute diarrhea in compare to control group (53.8 and 82.1%, $p < 0.05$).²⁵ The other group appointed that probiotics intake results up with decreased level of pro-inflammatory cytokines (TNF- α , IL-6, IL-10, IL-12, IL-17A, IL-17C and IL-22) in patients after surgical treatment of colorectal cancer, with significantly lower prevalence of acute diarrhea.^{26,27} The intake of *Enterococcus faecium* M-74 resulted with lower risk of severe neutropenia (crucial condition for NE) in patients with leukemia treated by chemotherapy.²⁸ In according to other post-chemotherapy complications, other randomized clinical trial appointed significantly lower occurrence of fever among pediatric patients ongoing chemotherapy.²⁹

The probiotics usage in NE is a dynamic topic of scientific research. Nevertheless, its intake in patients

isn't currently recommended according to current guidelines of numerous scientific associations including European Society of Medical Oncology³⁰ or German Society of Hematology and Medical Oncology³¹. The recent recommendations of European Society of Pediatric Gastroenterology, Hepatology and Nutrition appoint usefulness of probiotics in treatment and prevention of NE, but on the other hand they underline the need of further research on the particular strains.³²

Conclusion

The probiotics appeal as beneficial agents in both prevention and treatment of NE in according to their impact on gut immune barrier improvement. However older societies' guidelines were cautious, the most modern ones appoint probiotics as a promising agent in NE.

Declarations

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Author contributions

Conceptualization, J.G. and P.H.; Methodology, J.G.; Software, Ł.D.; Validation, P.H., J.G. and Ł.D.; Formal Analysis, J.G.; Investigation, J.G., P.H. and Ł.D.; Resources, J.G., P.H. and Ł.D.; Data Curation, J.G. and P.H.; Writing – Original Draft Preparation, J.G., P.H. and Ł.D.; Writing – Review & Editing, P.H., J.G.; Visualization, J.G.; Supervision, J.G.; Project Administration, J.G., P.H. and Ł.D.

Conflicts of interest

Authors have no conflicts of interest to declare.

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