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ORIGINAL ARTICLE

Clinical Trials Study

Intestinal-borne dermatoses significantly improved by oral application of *Escherichia coli* Nissle 1917

Elina Manzhalii, Daniel Hornuss, Wolfgang Stremmel

Elina Manzhalii, Department of Propedeutics of Internal Medicine 2, Bogomolets National Medical University, 02097 City of Kiev, Ukraine

Daniel Hornuss, Wolfgang Stremmel, Department of Gastroenterology, University Hospital of Heidelberg, 69120 Heidelberg, Germany

Author contributions: Manzhalii E is the responsible author, designed the study and performed the experiments; Hornuss D contributed by his expertise in colonic microbiota and Stremmel W wrote the manuscript.

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Correspondence to: Elina Manzhalii, MD, Department of Propedeutics of Internal Medicine 2, Bogomolets National Medical University, 02097 City of Kiev, Ukraine. wolfgang.stremmel@med.uni-heidelberg.de
Telephone: + 49-6221-568700
Fax: + 49-6221-564116

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Abstract

AIM: To evaluate the effect of oral *Escherichia coli* (*E. coli*) Nissle application on the outcome of intestinal-borne dermatoses.

METHODS: In a randomized, controlled, non-blinded prospective clinical trial 82 patients with intestinal-borne facial dermatoses characterized by an erythematous papular-pustular rash were screened. At the initiation visit 37 patients entered the experimental arm and 20 patients constituted the control arm. All 57 patients were treated with a vegetarian diet and conventional topical therapy of the dermatoses with ointments containing tetracycline, steroids and retinoids. In the experimental arm patients received a one month therapy with oral *E. coli* Nissle at a maintenance dose of 2 capsules daily. The experimental group was compared to a non-treatment group only receiving the diet and topical therapy. The primary outcome parameter was improvement of the dermatoses, secondary parameters included life quality and adverse events. In addition the immunological reaction profile (IgA, interleucin-8 and interferon-α) was determined. Furthermore the changes of stool consistency and the microbiota composition over the time of intervention were recorded.

RESULTS: Eighty-nine percent of the patients with acne, papular-pustular rosacea and seborrhoic dermatitis responded to *E. coli* Nissle therapy with significant amelioration or complete recovery in contrast

to 56% in the control arm ($P < 0.01$). Accordingly, in the *E. coli* Nissle treated patients life quality improved significantly ($P < 0.01$), and adverse events were not recorded. The clinical improvement was associated with a significant increase of IgA levels to normal values in serum as well as suppression of the proinflammatory cytokine IL-8 ($P < 0.01$ for both parameters). In the *E. coli* Nissle treated group a shift towards a protective microbiota with predominance of bifidobacteria and lactobacteria ($> 10^7$ CFU/g stool) was observed in 79% and 63% of the patients, respectively ($P < 0.01$), compared to no change in the control group without *E. coli* Nissle. Moreover, the detection rate of a pathogenic flora dropped from 73% to 14 % of the patients in the experimental arm ($P < 0.01$) with no significant change in the control arm (accounting 80% before and 70% after the observation period, $P > 0.05$). Accordingly, stool consistency, color and smell normalized in the *E. coli* Nissle treated patients.

CONCLUSION: *E. coli* Nissle protects the mucus barrier by overgrowth of a favorable gut microbiota with less immunoreactive potential which finally leads to clinical improvement of intestinal borne dermatoses.

Key words: Intestinal-borne dermatoses; *Escherichia coli* Nissle 1917; Immunological response; IgA; Interleukin-8; Interferon-α; Gut microbiota

Core tip: The occurrence of facial dermatoses with erythematous papular-pustular exanthemas is often linked to intestinal inflammation. However, the underlying mechanism remains unclear, and innovative treatment options are missing. Here we show that patients with these dermatoses carry a more aggressive microbiota associated with suppressed serum IgA levels, but increase of the proinflammatory cytokines interleukin-8 and interferon-α. Clinical manifestation, microbiota and inflammatory parameters are significantly improved by application of *Escherichia coli* Nissle. It indicates the usefulness of this probiotic therapy in a neglected patient population in desperate need for effective help.

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INTRODUCTION

Gastrointestinal diseases are often associated with facial dermatoses including acne, rosacea or seborrhoic dermatitis which impair the quality of life of these patients[1-3]. Common feature of these manifestations is an erythematous papular-pustular rash. The digestive system reveals in these cases often infections or an altered microbiota[1,4-8]. Some bacterial genera or species, *e.g.*, bacteroides, firmicutes or bifidobacteria, are predominant in comparison to others like *Escherichia coli* (*E. coli*), lactobacilli and enterococci[4,5,9-13]. Staphylococci, proteus and candida belong to the transient microflora[14]. The composition of the intestinal microbiota is mainly determined by dietary patterns[12]. The function of the microbiota has recently been the focus of scientific interest because it is not only responsible for maintaining a physiological immune response, but also for metabolic processes connected with insulin resistance, obesity and manifestation of fatty liver disease[1,2,8,15-17]. It has also been suggested that an intestinal micro-ecologic imbalance may cause dermatoses induced by an overstimulated immune system[17-19]. This could have therapeutic implications by changing the microbiota towards less aggressive bacterial colonization. One example is the oral application of the *E. coli* strain Nissle 1917 (EcN). By means of special adhesive organelles (by the type F-1A, F-1C and curly fimbriae), the strain has an ability to attach to the mucus membrane of the large intestine and to arrange as microcolonies, forming of a biofilm[20]. Due to the presence of flagella, the bacteria are also mobile, which gives them the advantage of colonizing the colon[21,22]. Therefore, these bacteria were shown to strengthen the mucosal barrier also by interacting with immune modulatory and anti-inflammatory mechanisms[23,24]. *E. coli* Nissle inhibits the growth of Gram-negative anaerobic bacteria by its secretion of antimicrobial substances (microcins) and by siderophores which capture iron and, thus, prevent the growth of certain pathological bacterial strain[16,25]. A postulated overstimulation of the immune system in intestinal disease-related dermatoses by a pathologic microbiota could be identified by elevation of cytokines and chemokines in the circulation[18,26]. Central players are interleukin-8 (IL-8) and α-interferon, which attract mononuclear cells to the site of inflammation to destroy pathogens by activation of the immune system[3]. Before a pathological microbiota invades the organism it has to pass the mucosal barrier. There are several lines of defense which have to be broken[3,26]. The mucus is the first hurdle which has to be taken. Within the mucus there is IgA which is known to inactivate invading bacteria. Since it is secreted from systemic sources, patients with IgA deficiency are prone to intestinal-borne infections[27].

Accordingly, in this study we evaluate the role of IL-8, interferon (INF)-α and IgA as players in the pathogenesis of intestinal disease related dermatoses and the effect of oral administration of *E. coli* Nissle in these conditions.

Table 1 Baseline characteristics of the study population

Characteristic	Experimental arm (n = 37)	Control arm (n = 20)
Sex (women)	63%	61%
Sex (male)	37%	39%
Age (yr)	29 ± 3.1	28 ± 2.5
Smoker	34%	36%
Oral contraception (women)	4%	5%

MATERIALS AND METHODS

In the randomized, controlled, non-blinded, prospective clinical trial 82 patients met the criterion of papular-pustular exanthema with facial manifestation. They were instructed to participate in a clinical trial, informed about the nature of the study and randomized by a closed envelope drawing to the experimental (EA) or control (CA) arm population. Between the evaluation and initiation visit (up to 4 wk interval), 4 and 21 of the participants in the EA and CA groups, respectively, were lost for the study population. The high loss of patients in the control arm was due to the information of the patients that they did not participate in active treatment protocol with *E. coli* Nissle. Thus, finally 37 patients entered the EA and 20 patients constituted the CA group. All included patients underwent physical examinations including the consultation of a dermatologist to verify the diagnosis of the skin dermatoses.

For basic treatment of chronic dermatoses, a diet with predominance of vegetable products was prescribed for all patients. The patients of the control arm (CA) only received standard topical therapy prescribed by a dermatologist, consisting of ointments containing tetracycline, steroids and retinoids (Kremgen® and Lokoid®). The patients of the experimental arm (EA) received a combination treatment which included the standard topical therapy of the dermatoses in combination with oral administration of *E. coli* Nissle 1917 (Mutaflor®): 1 capsule daily for 4 d, then 2 capsules daily for the following month. One capsule of the *E. coli* Nissle 1917 contained 2.5 - 25 × 10^9 live bacteria (CFU). The capsules are resistant to gastric juice and do not disintegrate before they reach the terminal small intestine. The patients were informed about the need to store the medication at a cool place. Follow-up examinations of the dermatoses were performed after a month. The therapeutic effect was estimated according to the dynamics of improvement of the dermatological manifestations. Another criterion was the subjective evaluation of the patients in regard to tolerability and adverse events. Life quality was measured by a scale of 4 index points including: good, acceptable, impaired and not acceptable. For testing of the immunological response in blood, a white blood cell (WBC) differentiation was performed, and the concentration of IL-8 and INF-α was determined by an immunoassay. IgA was quantified by an immunoassay method. The stool of the patients was evaluated in regard to its consistency, color, smell, mucus content and WBC.

Furthermore the stool neutral fat, fatty acid, starch content and presence of muscle fibers were determined[14]. Quantification of bacterial strains was performed by standard techniques[14]. The trial was approved by the local ethical committee.

Ethical permission

All study participants were informed about the study nature and signed a written consent form. The study protocol was approved by the regional committee for research ethics.

Statistical analysis

Statistical analysis performed by using SPSS-20 software. All data in this study were expressed as mean ± SD or percent. The Kolmogorov-Smirnov normality test was used for data distribution analysis. All the values had parametric distribution. Analysis of Variance was applied for multiple comparisons and if the results were significant, a post-hoc Turkey's test was performed. The comparison of the connected values namely the data from the same patient before and after treatment was done using the Student's *t*-test for paired samples. The differences between groups were considered significant at $P < 0.05$.

RESULTS

Out of 123 patients with dermatoses primarily evaluated, 82 patients revealed a papular-pustular exanthema with facial manifestation. Of these, 57 patients agreed to participate in the study and were finally included in the trial with an age range from 18 to 42 years, a disease duration range from 1 to 10 years, and a gender distribution of 35 women and 22 men. The experimental arm (EA) consisted of 37 and the control arm (CA) of 20 patients (Table 1).

All patients revealed the predominant feature of erythema in conjunction with papular-pustular elements. Twenty-two percent out of the patients were diagnosed with acne, 36% with papular-pustular rosacea and 57% with seborrhoic dermatitis. In 10% of the cases the entire facial skin was involved. Concerning the primary end point of the trial, the improvement of the dermatologic features was significantly greater in the EA compared to the CA group ($P < 0.01$). After one month, in the EA group 32% showed recovery and 57% significant amelioration (11% simple amelioration), whereas in the CA group only 17% revealed recovery and 39% significant amelioration (32% simple amelioration and 12% no change) (Figure 1).

The resolution of clinical manifestations of the inflammatory process of the facial skin occurred in

Table 2 Interferon-α, interleukin-8 and IgA in serum before and after treatment

Arms of the patients	INF-α, pg/mL		IL-8, pg/mL		IgA, g/L	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental arm (n = 37)	8.07 ± 2.97	3.73 ± 2.88[d, f]	30.8 ± 4.42	17.1 ± 0.65[d, f]	0.45 ± 0.05[b]	0.71±0.22[d, f]
Control arm (n = 20)	6.88 ± 1.77	6.12 ± 1.53	27.0 ± 2.72	25.2 ± 1.23[b]	0.35 ± 0.9	0.54 ±0.05[d]

[b]P < 0.01 and [d]P < 0.001 significant difference before *vs* after treatment; [f]P < 0.01 *vs* control arm after treatment. INF: Interferon; IL: Interleukin.

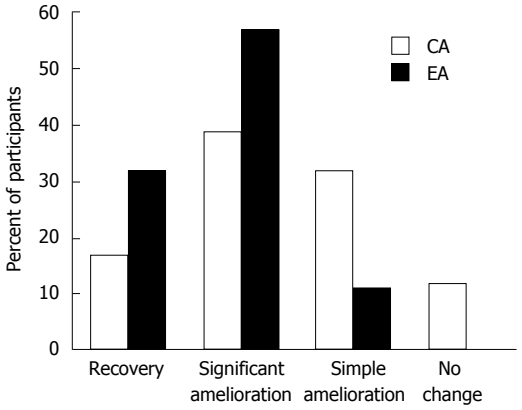

Figure 1 Improvement of dermatological features in both groups after 1 mo. Illustrated are the percentages of patients with facial dermatoses in the control arm (CA) and experimental arm (EA) over the time of the trial. They are categorized according to the degree of change in clinical manifestation.

the reversed order of their development. Initially, edema and swelling decreased, later papular rush and erythema faded as well as the formation of new papulae and pustulae discontinued. This was followed by disappearance of crusts in the area of the lesions, and nodular eruptions gradually flattened (Figure 2 as an example).

All patients in both groups tolerated the treatment very well, and adverse events were not recorded. All patients in the EA showed an increase of life quality by 1.7 ± 0.6 index points (< 0.01) revealing an acceptable or good condition in all patients of the EA group in contrast to the CA group with an overall unchanged impaired life quality (P > 0.05). Accordingly, *E. coli* Nissle showed high therapeutic efficacy in addition to good tolerability and absence of serious adverse reactions reported by the patients.

Elevated INF-α values showed a trend towards reduction in the EA patient population after therapy, but did not reach statistical significance. Low serum IgA levels were initially recorded in the EA and CA group. After treatment, the IgA level was normalized only in the EA arm (Table 2 and Figure 3). The same is true for the elevation of IL-8 cytokine levels which were normalized after treatment in the EA patient group. This is probably due to the immunomodulatory properties of *E. coli* Nissle 1917 which decreases the level of newly activated T-lymphocytes migration into the focus of inflammation. Accordingly, also the lymphocytosis disappeared in 78% of the EA group, whereas it improved in the CA group only in 42 % of the patients (Table 2 and Figure 3).

In regard to stool appearance, 82% of the patients initially had loose stools of grey color, sticky consistency with strong smell and mucus in large amounts. After treatment, 71% of participants in the EA had a formed stool of typical color and smell, and only small amounts of mucus.

Before treatment, bacteriological stool culture showed a decrease in the number of bifidobacteria and lactobacteria in both patient groups but an increase in potential pathogenic bacteria, *i.e.,* staphylococci, yeasts, bacteroides, proteus, citrobacter and klebsiellae (Table 3).

After therapy with *E. coli* Nissle (EA), an increase of bifidobacteria and lactobacteria in stool cultures was noted (P < 0.01 for both species). There was a significant decrease recorded in the number of staphylococci, yeasts, bacteroides, proteus, citrobacter, klebsieallae in 59% of the EA-patients as compared to no change in the CA-group (P < 0.01) (Table 3).

DISCUSSION

The mechanism by which intestinal diseases induce related dermatoses is obscure. Here we show that intestinal-borne dermatoses are accompanied by a shift towards a more aggressive intestinal microbiota spectrum. Due to their potential to invade the mucosal barrier, they activate the immune system with elevation of IL-8 and interferon-α. This could be the reason for induction of dermatoses because they attract mononuclear cells to preformed lesions of the skin, leading to inflammation. The dermatoses are significantly improved after oral application of *E. coli* Nissle. Whether the low IgA levels initially recorded in the patient population are the consequence or origin of invasion of pathogenic bacteria remains to be determined. However, the consumption of IgA within the mucus seems more likely because it returns to normal values after the treatment course.

In addition to the observed changes of the microbiota distribution, the biofilm of *E. coli* Nissle per se may also have an impact on stool consistency. It may be due to an effect on motility as well as the

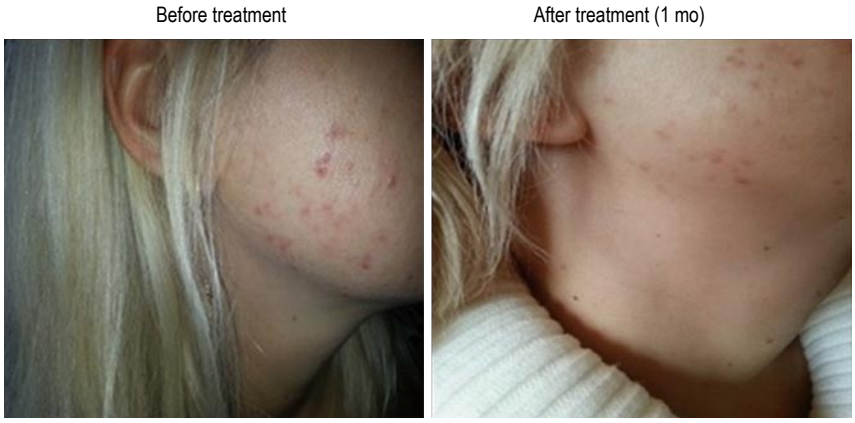

Figure 2 Female patient; EA group before and one month after treatment. Clinical example of a patient treated with *E. coli* Nissle. The facial popular-pustular exanthema was significantly improved over the 1 mo treatment period.

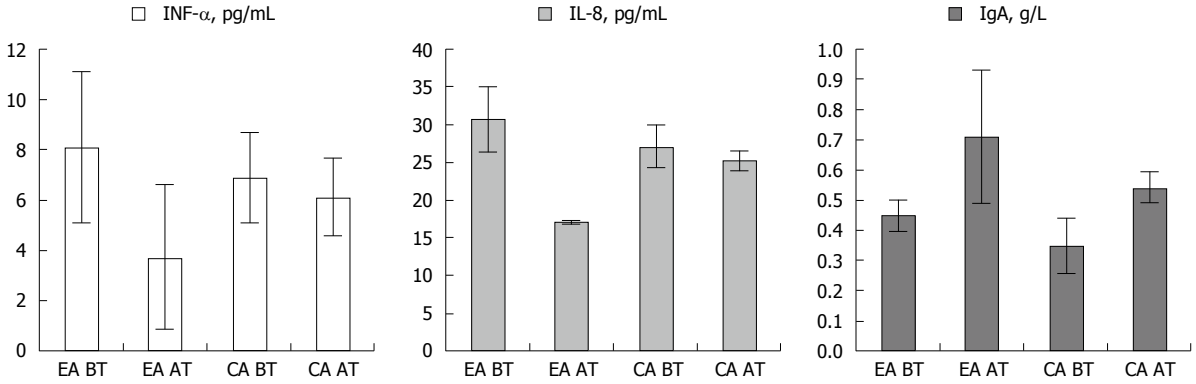

Figure 3 Improvement of serum levels of INF-α, IL-8 and IgA in experimental arm before (EA BT) and after treatment (EA AT), and control arm before (CA BT) and after treatment (CA AT). Serum INF-α, IL-8 and IgA levels over the trial course. Illustrated are the values of INF-α , IL-8 and IgA in the experimental arm before (EA BT) and after treatment (EA AT) and the control arm before (CA BT) and after treatment (CA AT).

Table 3 Changes of the flora after treatment with *E. coli* Nissle *n* (%)

Microflora characteristics	Experimental arm (n = 37)		Control arm (n = 20)	
	Before treatment	After treatment	Before treatment	After treatment
Bifidobacteria > 10^7 CFU/g	5 (14)	29 (79)[b]	3 (15)	3 (15)
Normal < 10^7 CFU/g	26 (70)	7 (19)[b]	15 (75)	14 (70)
Below normal absent	6 (16)	1 (2)[b]	2 (10)	3 (15)
Lactobacteria > 10^7 CFU/g	3 (8)	23 (63)[b]	3 (15)	2 (10)
Normal < 10^7 CFU/g	27 (73)	13 (35)[b]	15 (75)	15 (75)
Below normal absent	7 (19)	1 (2)[b]	2 (10)	3 (15)
Pathogenic microflora	27 (73)	5 (14)[b]	16 (80)	14 (70)

[b]$P < 0.01$ significant difference before *vs* after treatment.

functionality of the mucus barrier. The production of short-chain fatty acids increases the nutritional state of the mucus and thus its capability to absorb water[14,20]. This improves the motility as well as the absorption of water and sodium. All of this helps to form a more consolidated stool. More importantly, because the mucosal barrier is strengthened, pathogens cannot easily penetrate and, thus, the *E. coli* Nissle application prohibits systemic activation of the immune system eventually inducing intestinal-borne dermatoses.

In conclusion, we report that *E. coli* Nissle is very effective to treat intestinal-borne chronic dermatoses. It shows good tolerability and no adverse events. The mode of action relates to change of the intestinal microbiota towards less aggressive bacteria. This in turn ameliorates the immune response characterized by a normalization of IgA and IL-8. Thus, it represents a treatment option for patients with intestinal borne dermatosis.

COMMENTS

Background

Intestinal-borne dermatoses have unknown etiology and there is a medical need for their therapy. The recent observation that the gut microbiota has impact on the immune system guided us to the question whether this induces

dermatoses and whether microbiota modulation may be of therapeutic use.

Research frontiers

The present study focuses on etiology and therapy of intestinal dermatoses as a neglected field in gastroenterology, although a large number of patients suffer from this entity. It covers the areas of microbiota and the associated systemic immune response.

Innovations and breakthroughs

It is an innovative approach to link the gut microbiota to the pathogenesis of intestinal-borne dermatoses. The fact that modulation of the microbiota by application of *Escherichia coli* (*E. coli*) Nissle 1917 improves the dermatoses was unexpected and opens a new avenue of therapy for these patients in need.

Applications

The study provides a rationale for the therapy of intestinal-borne dermatoses. Indeed it is shown that *E. coli* Nissle 1917 improves these dermatoses by suppressing the intestinal microbiota-triggered immune response. It will open avenues of new therapies also with other microbiota-modulating regimens. The study may also stimulate basic research to unravel the interaction of the gut microbiota and the immune system.

Terminology

The paper deals with different intestinal-borne dermatoses, the adaptive immune response mechanism, the composition of the gut microbiota in regard to protective and aggressive bacterial colonization and the biological activity of *E. coli* Nissle 1917.

Peer-review

The manuscript is very interesting for the readers.

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