Translated by E.V. Trushina

Research Article

https://doi.org/10.23934/2223-9022-2024-13-2-212-225

The Role of Intestinal Translocation in the Pathogenesis of Pneumonia in Acute Poisoning and the Contribution of Intestinal Lavage to Its Prevention and Resolution

V.A. Matkevich[1, 2, 3] ✉, T.T. Tkeshelashvili[1], A.G. Vorobyova[1], N.E. Stolbova[1], M.M. Potskhveriya[1, 2], Yu.S. Goldfarb[1, 2]

Department of Acute Poisoning and Somatopsychiatric Disorders
[1] N.V. Sklifosovsky Research Institute for Emergency Medicine
Bolshaya Sukharevskaya Sq. 3, Moscow, Russian Federation 129090
[2] Russian Medical Academy of Continuing Professional Education
Barrikadnaya Str. 2/1, bldg. 1, Moscow, Russian Federation 125993
[3] Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of the Federal Medical and Biological Agency of Russia
Malaya Pirogovskaya Str. 1, bldg. 3, Moscow, Russian Federation 119435

✉ **Contacts:** Victor A. Matkevich, Doctor of Medical Sciences, Scientific Consultant, Department of Acute Poisoning and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: matkevich@mail.ru

RELEVANCE Among the deadly complications of severe poisoning, pneumonia occupies a leading position, and therefore the search for new solutions aimed at prevention and treatment of this complication is relevant.

AIM OF THE STUDY To study the role of intestinal translocation in the pathogenesis of pneumonia in acute poisoning and to evaluate the contribution of intestinal lavage to its prevention and resolution.

MATERIAL AND METHODS Here at the N.V. Sklifosovsky Research Institute for Emergency Medicine, we analyzed the outcomes of treatment of 1124 patients with severe oral poisoning: by psycho-pharmacological drugs (PPD) — 172 and corrosive substances (CS) — 325 people; with intravenous administration of methadone (M) — 575, as well as 50 patients with alcoholic delirium (AlD) as a complication of PPD and CS poisoning.

In cases of PPD and M poisoning, the patients' Glasgow Coma Scale (GCS) scores ranged from 3 to 5, with respiratory disorders requiring mechanical ventilation.

The severity of CS poisoning was due to the 2nd-3rd degree chemical burn of the mucous membrane of the mouth, pharynx, esophagus and stomach. The condition of patients with AlD was severe and corresponded to 29.0 (27.0; 30.0) points on the DELIRIUM RATING SCALE – R – 98.

In cases of PPD and CS poisoning, the state of the intestinal microbiocenosis, the permeability of the intestinal barrier, the endotoxin content of gram-negative bacteria in the blood and integral indicators of intoxication were studied. Intestinal lavage (IL) was used in the observed groups (655). Patients in the comparison groups (469) received standard therapy.

RESULTS Initially detected: intestinal dysbiosis of II–III degree, increased permeability of the intestinal barrier — 3.8–4.9 times higher than normal, a tenfold increase in the content of endotoxin in the blood and a 6-fold increase in the leukocyte index of intoxication.

It was established that intestinal lavage effectively cleanses the entire gastrointestinal tract, eliminates intestinal dysbiosis, reduces excessive permeability of the intestinal wall, and is accompanied by a 2-fold decrease in the endotoxin content in the blood and the leukocyte index of intoxication. As a result, pneumonia was registered in cases of PPD poisoning 2.1; M —1.9; CS — 2.4, and AlD — 9.8 times less often than in the comparison groups. Mortality among the patients with PPD poisoning decreased by 7 times, and with M and CS poisoning, as well as with AlD, there were no deaths, while in the respective comparison groups, the mortality rate for pneumonia was 5.1, 7.4, and 17.4%, respectively. The differences were statistically significant.

CONCLUSION A pattern in the form of intestinal dysbiosis, excessive permeability of the intestinal barrier, and increased levels of endotoxin in the blood may indicate that the source of the infectious-inflammatory process in the lungs during acute poisoning is the intestine; and the cause-and-effect relationship between the sanitation of the gastrointestinal tract by intestinal lavage and a reduction in the incidence of pneumonia and mortality confirms this hypothesis.

Keywords: acute poisoning, pneumonia, pathogenesis, intestinal lavage, prevention of pneumonia

For citation Matkevich VA, Tkeshelashvili TT, Vorobyova AG, Stolbova NE, Potskhveriya MM, Goldfarb YuS. The Role of Intestinal Translocation in the Pathogenesis of Pneumonia in Acute Poisoning and the Contribution of Intestinal Lavage to Its Prevention and Resolution. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2024;13(2):212–225. https://doi.org/10.23934/2223-9022-2024-13-2-212-225 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study had no sponsorship

Affiliations

Victor A. Matkevich	Doctor of Medical Sciences, Scientific Consultant, Department of Acute Poisoning and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Associate Professor, Department of Clinical Toxicology, Russian Medical Academy of Continuing Professional Education; Leading Researcher, Laboratory of Toxicology, Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine; https://orcid.org/0000-0001-6765-6619, matkevich@mail.ru; 25%, development of the concept and design of the study, structuring the text and drafting the manuscript

Tengiz T. Tkeshelashvili	Head, Department of Resuscitation and Intensive Care for Emergency Detoxification, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-4990-1363, tkesh00@gmail.com; 23%, collection of clinical material according to the study design, its statistical processing and analysis, approval of the final version of the article, responsibility for the integrity of all parts of the article
Alena G. Vorobyova	Toxicologist, Department of Acute Poisoning and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0009-0003-8580-6002, alena_vorobeva_90@list.ru; 15%, collection of clinical material in accordance with the study design, its analysis and interpretation
Natalya E. Stolbova	Chief Physician, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-2666-0560, stolbovane@sklif.mos.ru; 15%, collection of clinical material in accordance with the study design, mathematical processing and analysis of the data obtained
Mikhail M. Potskhveriya	Doctor of Medical Sciences, Head, Department of Acute Poisoning and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Professor, Department of Clinical Toxicology, Russian Medical Academy of Continuing Professional Education; https://orcid.org/0000-0003-0117-8663, potskhveriyamm@sklif.mos.ru; 2%, research design development and organization, text editing
Yuriy S. Goldfarb	Doctor of Medical Sciences, Full Professor, Head, Department of External Scientific Relations; Researcher, Department of Acute Poisoning and Somatopsychiatric Disorders, N.V. Sklifosovsky Research Institute for Emergency Medicine; Head, Department of Clinical Toxicology, Russian Medical Academy of Continuing Professional Education; https://orcid.org/0000-0002-0485-2353, goldfarbjs@sklif.mos.ru; 10%, adjusting the study design, final editing of the text

AP — acute poisoning
BOS — bacterial overgrowth syndrome
CS — corrosive substances
CVS — cardiovascular system
DT — delirium tremens
ES – enteral solution
GCS — Glasgow Coma Scale
GIT— gastrointestinal tract
IFS — intestinal failure syndrome
IL — intestinal lavage
IMP — intravenous methadone poisoning
L — lactulose
LII — leukocyte intoxication index
LPS — lipopolysaccharide (endotoxin)
M — mannitol
MV — mechanical ventilation
NEA — normal enzymatic activity
NII — non-occlusive intestinal infarction
NSI —neutrophil shift index
PAMPs — Pathogen-associated molecular patterns (LPS, bacterial DNA and RNA, flagellin, lipoteichoic acid, lipopeptides, peptidoglycan, and (1→3)-β-D-glucan)PCS — poisoning by corrosive substances
PPD — psychopharmacological drugs
PPPD — poisoning by psychopharmacological drugs
SIR — systemic inflammatory response

INTRODUCTION

The most common and life-threatening complication of severe acute poisoning (AP) is pneumonia. According to a number of authors, the incidence of pneumonia, for example, in case of poisoning by psychopharmacological drugs (PPD) is 25–49.4%, and the mortality rate reaches 60 % [1–4]. In this regard, the analysis of the causes of pneumonia development as a complication of AP, and the search for a new way to prevent it and reduce mortality deserve special attention.

The onset of pneumonia, as a rule, coincides with toxicogenic stage, and is fully manifested at the somatogenic stage of AP [5]. Among the causes of pneumonia in critical conditions, the most commonly cited are: disorders of external respiration and drainage function of the bronchopulmonary system in disorders of consciousness (coma, delirium), nosocomial infection, tracheal intubation and prolonged mechanical ventilation (MV), as well as catheter-related infections [6–8]. The routes of infection into the lungs are bronchogenic, hematogenous and lymphogenous ones [9]. Researchers consider disturbances in homeostasis indicators (hemorrheology, lipid peroxidation and antioxidant system, immunity, etc.) as components

of the pathogenesis of pneumonia in acute poisoning [10–14].

Along with generally accepted views on the development of pneumonia, scientific publications discuss the possibility of contamination of internal organs, including the lungs, from the intestine due to the translocation of microbial cells and their toxins in case of pathologically increased permeability of the intestinal barrier [15–19].

The leading role is given to gram-negative intestinal bacteria that form an endotoxin-lipopolysaccharide (LPS) — a structural component of the cell wall that can have a cytotoxic and immunosuppressive effect and trigger a cascade of septic reactions in the body [20–22].

In case of severe poisoning, all conditions are created (hemoperfusion disorders in the intestinal wall, its paresis, etc.) for pathologically increased permeability of the intestinal barrier and the development of enterogenous toxemia [23, 24].

We have noticed that among patients with severe oral poisoning, who underwent intestinal lavage (IL) as part of treatment measures for the purpose of enteral detoxification, complications of an infectious-inflammatory nature, including pneumonia, developed less frequently, which prompted an in-depth study of this phenomenon in acute poisoning.

Aim: to study the role of intestinal translocation in the pathogenesis of pneumonia in acute poisoning, and to evaluate the contribution of intestinal lavage to its prevention and resolution.

MATERIAL AND METHODS

We analyzed the treatment outcomes of 1124 patients of various nosological forms from four independent cohorts treated at the Department of Acute Poisoning and Somatopsychiatric Disorders of the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2012–2022, including 172 with severe acute oral poisoning by psychopharmacological drugs (PPPD), 325 with poisoning by corrosive substances (PCS), 575 with intravenous methadone poisoning (IMP), and 52 with delirium tremens (DT) complicating PPPD in 18 cases and PCS in 34 cases.

In the cohort with PPPD, out of 172 patients, there were 39.5% men and 60.5% women, the mean age being 39 (26.0:52.0) years. This type of severe poisoning was characterized by depression of consciousness – a Glasgow Coma Scale (GCS) score of up to 3-5, and mixed-type external respiration disturbances.

Among 325 patients with PCS, 65.9% were men and 34.1% were women. Of the total number, 35.7% of patients were with acetic acid poisoning, and 64.3% - with alkali (sodium hydroxide) poisoning. The mean age of the patients was 43 (33.0:56.0) years. The condition of patients with PCS was severe due to chemical burns of the mucous membrane of the mouth, pharynx, esophagus and stomach of the 2nd-3rd degree according to the classification of S.V. Volkov et al. (2005). Diagnosis of the burn and subsequent monitoring of the condition of the mucous membrane of the gastrointestinal tract (GIT) was carried out using esophagogastroduodenoscopy.

The cohort with IMP included 575 patients with poisoning as a result of an overdose during intravenous administration of the drug for the purpose of drug intoxication, which was accompanied by depression of consciousness (a GCS score of 5-7) and mixed breathing disorders with periods of apnea. There were 83.8% men, 16.2% women, their mean age was 32 (29.0: 36.0) years.

In the cohort of 52 patients with DT, there were 96.2% men and 3.8% women with mean age of 53 (40.0: 65.0) years; in 34.6% of cases DT developed against the background of PPPD and in 65.4 % — PCS. To assess the severity of delirium, the DELIRIUM RATING SCALE – R – 98 was used, in order to calculate the sum of points on 13 items [25]. When choosing an answer option, in addition to data from direct examination of the patient, information from all available sources (medical staff, family, medical documentation) was taken into account. At the peak of clinical manifestations of delirium, the total score in the study group was 29.0 (27.0: 30.0), and in the comparison group - 28.0 (26.0: 29.0). In the absence of signs of delirium, the patients' condition corresponded to 5.0 (4.0: 6.0) points.

In order to study the state of intestinal microbiocenosis, 50 patients (males - 76.0%, and females - 24.0%) aged 42 (36: 52) years with PPPD and PCS were examined, and the composition of the fecal microflora was assessed. The microbial composition of feces was determined by the bacteriological method. The sample for the test was taken from the first portion of feces during IL, marking it as “initial”, and then on the 5th day during spontaneous defecation. In patients of the comparison groups, the fecal sample taken on the 1st day was labeled as “initial”. The second sample for

testing was also taken on the 5th day. Thus, 2 samples were taken from all the 50 patients, and 10 microorganisms were determined in each biosample. A total of 1000 tests were conducted.

To assess the degree of disturbances in the luminal microflora, we used the classification of dysbiosis given in "Protocol for the management of patients. Intestinal dysbacteriosis" industry standard, according to which: grade I is characterized by a decrease in the content of bifidobacteria to 108–6 and/or lactobacilli to 107–6 CFU/g of feces, typical Escherichia to 106–5 or an increase in the number of E. Coli more than 108 CFU/g of feces; grade II: a decrease in the content of bifidobacteria and lactobacilli, the presence of opportunistic flora at a concentration of 105 CFU/g of feces and higher, or associations of opportunistic microorganisms in an amount of 103–104 CFU/g of feces; grade III: associations of opportunistic microorganisms in high titers and a decrease in the content of bifidobacteria and lactobacilli [26].

The results were assessed by comparing the number of patients in the groups that had deviations in the composition of certain microorganisms (their specific gravity) before the start of treatment and on the 5th day.

In order to study the state of intestinal barrier permeability, 40 patients (67.5% women and 32.5% men) were examined, of which 20 patients (Group I) with PCS and 20 patients (Group II) with severe acute oral PPPD.

The examination of intestinal wall permeability was carried out using the following method. After a single dose of a solution containing 1 g of lactulose (L) and 5 g of mannitol (M) in 120 ml of water, their concentration in a single portion of urine was determined using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) using Agilent 1260 (a chromatograph) and Sciex 6500+ (a MS/MS spectrometer). L and M concentrations were expressed in mg/L. The L/M concentration ratio was calculated, the reference value of which according to Simon D. Johnston et al. (2000) is 0.024 [27]. The degree of permeability of the intestinal barrier was assessed by the L/M value. A total of 80 tests were performed. L and M substances for the preparation of the solution were of pharmacopoeial quality. The trial points were: before the start of treatment and after 5 days.

To study the state of microbiocenosis and intestinal permeability, the groups of patients (with PCS and PPPD) were divided into two subgroups: I-a and II-a; I-b and II-b respectively. In target subgroups I-a and I-b, the patients received IL in addition to standard treatment. In the comparison subgroups - II-a and II-b, - the patients received only standard therapy, and in subgroup II-b (PPPD), in addition, hemodiafiltration was performed for the purpose of detoxification.

In order to establish the fact of translocation of intestinal microbial toxins, the content of LPS (endotoxin) in the blood serum was determined in 23 patients with PPPD using a modified method of LAL test (Evdokimova et al., 2009) [28].

The severity of endogenous intoxication in patients with PPPD was assessed using the leukocyte intoxication index (LII) according to Ya.Ya. Kalf-Kalif (1941), and the neutrophil shift index (NSI) (A.M. Kapitanenko, I.I. Dochkin, 1985).

The age and gender of the patients in the comparison group corresponded to those of the patients in the study group. The distribution of the total number of patients by nosological forms and comparison groups is presented in Table 1.

Table 1

Distribution of patients by nosological forms and comparison groups

No.	Nosological form	Groups of patients	Number of patients in groups	Total number of patients
1	PPPD	Study Comparison	122 50	172
2	IMP	Study Comparison	330 245	575
3	PCS	Study Comparison	170 155	325
4	DT	Study Comparison	33 19	52
Total:				1124

Notes: DT – delirium tremens; IMP – intravenous methadone poisoning; PPPD — poisoning by psychopharmacological drugs; PCS – poisoning by corrosive substances

All the patients underwent standard clinical, laboratory and instrumental examination; including for the purpose of monitoring lung function, all the patients underwent repeated chest radiography.

Patients in the study groups (655), in addition to the standard therapy, underwent IL using an enteral

solution (ES) according to the method of V.A. Matkevich (2012). For the patients with PPPD, IMP and DT, the solution was heated to 37–38° C and administered through a nasogastric dual-channel tube in portions of 150–200 ml every 5 minutes. The head of the bed for those patients was raised by 30–45 degrees. After administration of 1.5–2.5 liters of solution, loose stools appeared. In cases of absence of spontaneous bowel movements after administration of 2.5 liters of solution, pharmacological stimulation of the gastrointestinal tract was performed. IL was continued until the rinsing water was clean, and the total volume of the solution could range from 70–80 (for IMP and DT) to 500 ml/kg (for PPPD) of the patient's body weight. To collect intestinal secretions, a rectal probe with a colostomy bag was installed. The IL procedure, depending on the volume of ES, lasted 3–6 hours.

In patients with PCS, IL was started after the administration of painkillers and antispasmodics and gastric lavage. The ES temperature in these cases was 18–22 o C. The patients drank it in 200 ml portions every 5 minutes. The total volume of the solution used ranged from 3 to 4.5 liters. In cases where patients, due to the severity of their condition, were initially unable to take ES on their own, it was administered through a nasogastric tube.

At the first signs of DT, the decision to perform IL was made urgently. Before installing a nasogastric two-channel tube for the ES introduction, premedication was given: propofol (1.5–2.5 mg/kg of the patient's body weight), atropine (0.5 mg), listenone (100 mg), then, in order to prevent aspiration of gastric contents, tracheal intubation was performed, and the patient was transferred to mechanical ventilation. Subsequently, mechanical ventilation was continued according to indications. Basic therapy – drug sedation (sodium thiopental, 100 mg/hour; propofol, 50 mg/hour), as well as vitamin therapy, infusion and symptomatic therapy – were carried out in accordance with clinical recommendations.

Statistical processing of results

Statistical processing of the material was performed using the IBM SPSS Statistics 26.0. The normality of the data distribution was assessed using the Shapiro–Wilk test (n≤50). If the sample distribution differed from normal, the median (Me), 25th and 75th percentiles were determined in the form of Me (Q1; Q2). Categorical data are presented as n (%). To compare medians between the groups, the Mann–Whitney U test (M–W test) was used (independent groups). To compare qualitative data between the groups, Pearson's $\chi 2$ test and Fisher's exact test were used. If the sample was normally distributed, the Student's t-test was used. The level of statistical significance was taken to be $p<0.05$.

RESULTS

The patients tolerated the IL procedure satisfactorily; there were no adverse reactions or complications.

In the group of patients with PPPD as a result of IL, cleansing of the gastrointestinal tract occurred in 95% of cases within 3–6 hours; and in the comparison group, stool was achieved due to pharmacological stimulation of the intestine for 3 days in only 10% of patients. Moreover, the stool was fecal in nature, which meant incomplete cleansing of the intestines.

The period of restoration of clear consciousness (GCS score of 15) in the study group was on average 34 hours, and the period of mechanical ventilation relevance was 22.3 hours shorter than in the comparison group with a statistically significant difference ($p<0.05$).

In case of IMP, the use of IL ensured cleansing of the gastrointestinal tract within 3–6 hours in 100% of cases. In the comparison group, despite pharmacological stimulation, it was not possible to restore the propulsive function of the patients' intestines during the first 24 hours. During IL and in the immediate hours after it, the patients' condition gradually improved, and the degree of confusion decreased. Due to the emergence of attempts at spontaneous breathing, the mechanical ventilation modes were changed, followed by the transfer of the patients to spontaneous breathing. The periods of restoration of clear consciousness (GCS score of 15) and the relevance of mechanical ventilation in the study group were on average 13 hours shorter than in the comparison group.

Patients with PCS tolerated the IL procedure satisfactorily; no adverse reactions or complications were observed.

The condition of patients with DT improved, and regression of delirium symptoms began within 1 day after IL. In the study group, the duration of DT was 2.0 (1.0: 2.5) versus 5.0 (3.0: 6.5) days in the comparison group ($p<0.05$; M–W test).

A study of microbiocenosis in patients with PPPD and PCS showed that deviations in the microbial

composition of feces before the start of treatment were of the same type. In each of the four subgroups, some patients initially showed a two- to three-fold decrease in the titer of bifidobacteria and lactobacilli, increase in the titer of opportunistic flora to 105 CFU and higher, and S. aureus in stool samples. A comparative analysis of the rate and nature of microbial composition disorders in the initial samples of patients of the compared groups showed that in some areas their deviations from the norm were comparable, and in others they were quantitatively different, but these differences were not statistically significant.

Table 2 shows the composition of the intestinal microflora of patients with PCS from I-a and II-a subgroups.

As can be seen from the table, initially there were qualitative and quantitative changes in the composition of the microbiota in group I-a. The proportion of patients with a several-fold reduced titer of bifidobacteria in the initial samples was 58.3%; a decrease in the content of lactobacilli was recorded in 4 cases (33.3%). In group II-a, the proportion of patients in the same positions was 60%. At the subsequent stage of the study, the titer of both bifidobacteria and lactobacilli was reduced in group I-a only in 16.7% of patients, that is, the proportion of such patients was 3.5 and 2 times less, respectively, than before IL; and in group II-a - in 40 and 50%, respectively, that is, the proportion of patients with a reduced titer of bifidobacteria and lactobacilli decreased only by 1.5 and 1.2 times compared to the initial values. In group I-a, the titer of *Klebsiella spp*. was initially elevated in 4 observations (33.3%). After 5 days, an increased concentration of *Klebsiella* was determined only in 2 (16.7%) cases. *Staphylococcus aureus* was found in one patient during the first testing; subsequently, after IL, it was absent. A similar situation was observed when assessing the content of *K. pneumoniae.*

A decrease in the number of Escherichia coli with normal enzymatic activity was initially detected in 41.7% of cases; the proportion of such patients after 5 days was only 16.7%, which is 2.5 times less than the initial one. In the remaining patients, the population of these microorganisms was restored to normal numbers. An increased titer of *Candida spp.* was initially noted in 33.3% of cases; at the subsequent stages of the research, no patients with excessive titers of these fungi were found.

Table 2

Results of bacteriological examination of feces in group I-a and II-a patients with poisoning by corrosive substances

No.	Microorganisms and their quantitative characteristics	Groups of patients, stages of research and proportion of observations					
		II-a (n=12) Absolute number (%)			II-a (n=10) Absolute number (%)		
		Initial	5th day	Δ,%	Initial	5th day	Δ,%
1	*Bifidobacterium spp.* ↓	7 (58.3)	2 (16.7)	71.4	6 (60)	4 (40)	33.3
2	*Lactobacillus spp.* ↓	4 (33.3)	2 (16.7)	50.0	6 (60)	5 (50)	-16.7
3	*Klebsiella spp.* ↑	4 (33.3)	2 (16.7)	-50.0	5 (50)	3 (30)	-40
4	*S. aureus***	1 (8.3)	–		2 (20)	1 (10)	-50
5	*Enterococcus spp.*	–	–		–	–	
6	*K. pneumoniae* ↑	1 (8.3)	–		2 (20)	1 (10)	-50
7	*E. coli* с NEA* ↓	5 (41.7)	2 (16.7)	-60.0	4 (40)	4 (40)	0
8	*E. coli* lactose-negative ↑	2 (16.7)	–		2 (20)	2 (20)	0
9	*Proteus spp.* ↑	1 (8.3)	–		1 (10)	–	
10	*Candida spp.* ↑	4 (33.3)	–		3 (30)	2 (20)	-33.3

Notes: "–" normal values; ↓ – titer is reduced relative to normal values; ↑ – the titer is increased relative to normal values; * – *E. coli* with normal enzymatic activity (NEA); ** – this does not normally occur

Thus, as a result of assessing the quantitative and qualitative composition of the intestinal microbiocenosis, it was revealed that group I-a patients initially had dysbiotic disorders corresponding to grade II–III. On the 5th day after IL, the content of bifidobacteria in feces reached normal values in 71.4%, and lactobacilli - in 50% of patients who had an initially reduced titer. While the initially increased content of the representatives of opportunistic flora decreased to normal values. This dynamics indicated a positive effect of IL on the composition of the luminal flora of the intestine.

An assessment of the state of the intestinal microbiocenosis in patients of group II-a showed that initially, they, just like patients of group I-a, had dysbiotic disorders of varying degrees. The proportion of patients with a reduced titer of bifidobacteria and lactobacilli was 60%. After 5 days, during a repeated study, a decrease in the concentration of bifidobacteria was observed in 40%, and lactobacilli - in 50% of patients. An increased titer of Klebsiella spp. was detected initially in 50% of cases, and after 5 days - in 30% of cases. *Staphylococcus aureus* was isolated in 2 patients, and after 5 days – in one. *K. pneumoniae* was also initially detected in 2 cases, and upon re-examination – in one patient. A decrease in the content of *Escherichia coli* with normal enzymatic activity was initially detected in 5 patients, and after 5 days - in 4. An increased titer of lactose-negative *Escherichia* was initially detected in 20% of cases; when repeated after 5 days, the result remained the same. An increased titer of *Candida spp.* was detected in 30% of observations, after 5 days - in 20% of cases.

Thus, the results of the study showed that IL in patients with PCS promotes the elimination of opportunistic pathogens and the growth of fermented milk flora, while standard therapy does not have a significant corrective effect on the excess of opportunistic pathogens and the lack of fermented milk flora.

Table 3 shows the composition of the fecal microflora in group I-b and II-b patients with PPPD.

As can be seen from the table, in group I-b there was initially a decrease in the titer of bifidobacteria in 50% of patients, and the content of lactobacilli in 66.7%. On the 5th day after IL, the proportion of patients with a reduced titer of bifidobacteria and lactobacilli was 16.7% and 22.2%, respectively, which was 3 times less than the initial indicator with a statistically significant difference ($p<0.05$).

Table 3

Results of bacteriological examination of feces in group I-b and II-b patients with poisoning by psychopharmacological drugs

No.	Microorganisms and their quantitative characteristics	Groups of patients, stages of research and proportion of observations					
		I-b (n=18) Absolute number (%)			II-b (n=10) Absolute number (%)		
		Initial	5th day	Δ,%	Initial	5th day	Δ,%
1	*Bifidobacterium spp.* ↓	9 (50)	3 (16.7) [1]	-66.7	6 (60)	5 (50)	-16.7
2	*Lactobacillus spp.* ↓	12 (66.7)	4 (22.2) [2]	-66.7	8 (80)	6 (60)	-25
3	*Klebsiella spp.* ↑	3 (16.7)	1 (5.6)	-66.7	5 (50)	3 (30)	-40
4	*S. aureus***	3 (16.7)	–		4 (40)	3 (30)	-25
5	*Enterococcus spp.*	1 (5.6)	–		–	–	
6	*K. pneumoniae* ↑	1 (5.6)	–		5 (50)	2 (20)	-60
7	*E. coli* c NEA* ↓	2 (11.1)	1 (5.6)	-50.0	6 (60)	5 (50)	-16.7
8	*E. coli* lactose-negative ↑	2 (11.1)	–		3 (30)	2 (20)	-33.3
9	*Proteus sp.* ↑	1 (5.6)	1 (5.6)	0	1 (10)	–	
10	*Candida spp.* ↑	1 (5.6)	–		3 (30)	–	

Notes: statistical significance of the difference with the original indicator ([1] — $p<0.05$ according to the χ^2 criterion; [2] — according to the Fisher exact probability criterion). ˝–˝ normal values; ↓ — titer is reduced relative to normal values; ↑ — the titer is increased relative to normal values; * — E. coli with normal enzymatic activity; ** — this does not normally occur. c NEA* — normal enzymatic activity

The titer of *Klebsiella spp*. was initially increased in 16.7% of cases. On the 5th day, it remained elevated in only 5.6% of the same patients. An increased titer of K. pneumoniae before IL was determined in one patient. 5 days after IL it decreased to normal values.

It should be noted that S. aureus, initially isolated in 16.7% of cases, was not detected after IL. *Enterococcus spp*. was detected before IL in one patient; at the next stage of the research, there was no increased growth of these microbes.

A decrease in the content of *E. coli* with normal enzymatic activity upon admission to the hospital was noted in 2 patients. After IL, in one patient the number of *E. coli* reached normal values, while in the other it remained reduced.

The content of lactose-negative *E. coli* was initially increased in 11.1% of patients; on the 5th day they were not detected. Contents of *Candida spp*. was initially elevated in one patient, and on the 5th day their titer was normal.

Thus, as a result of examination of the state of intestinal microbiocenosis in patients with PPPD, grade II–III dysbacteriosis was found. The data obtained showed that IL had a corrective effect on the quantitative and qualitative composition of the intestinal microbiocenosis. The proportion of patients with an initially reduced number of bifidobacteria and lactobacilli decreased by 3 times on the 5th day after IL; and the proportion of patients with an initially elevated titer (105 CFU/g feces and higher) of opportunistic flora for some types of microorganisms (*Klebsiella spp*.) decreased by 3 times; and for other species, except *Proteus spp*., there was a normalization of quantitative and quality composition.

Initially, in patients of group II-b, just as in group I-b, abnormalities were identified that indicated the presence of dysbacteriosis. Upon admission of the patients to the hospital, there was a several-fold decrease compared to the norm in the titer of bifidobacteria in 6 (60%) and lactobacilli in 8 (80%) cases. During repeat examination after 5 days, the proportion of patients with reduced concentrations of bifidobacteria and lactobacilli remained virtually unchanged. Thus, the proportion of patients with a reduced titer of bifidobacteria on the 5th day was 50%, and 60% of patients had a low content of lactobacilli. In 50% of group II-b patients, an increase in the titer of Klebsiella spp. was detected; upon repeated testing, their titer was high in 30% of patients. *Staphylococcus aureus* was detected in 40% of patients from this group. After 5 days it was re-detected in 30% of patients. A decrease in the concentration of *Escherichia* with NEA was detected initially in 60% of observations, and at the next stage of the research - in 50% of cases. Overgrowth of *Candida spp*. during the first testing was observed in 3 patients; subsequently, they did not have elevated titers of yeast-like fungi.

Thus, the results of the research showed that patients of all the groups, both with PCS and PPPD, initially showed signs of dysbiosis, manifested in a two-three-fold decrease in the content of lactic acid flora and typical *Escherichia* in fecal samples, and an increase in titers of opportunistic species above 105 CFU/g. In addition, in 8–40% of cases in various groups, S. aureus was detected, which should not be normally present. The identified changes in the microbial composition of feces corresponded to grade II–III according to the classification of dysbiosis [26].

In the groups of patients who underwent IL, on the 5th day a significant decrease in the initially increased titer of opportunistic microorganisms was recorded until their complete disappearance. Along with this, on the 5th day after IL, the proportion of patients who initially had a reduced titer of lactoflora decreased by 50–71.4% in PCS, and by 66.7% in PPPD. Therefore, in this part of the patients, the content of normal microflora increased during the 5 days after IL and reached normal values.

The results of the study of intestinal permeability showed that in all observed patients with PCS and PPPD, the L/M ratio before the start of treatment was increased relative to the reference value: in subgroups I-a and II-a (PCS) this excess was 4.3 and 4.4 times, and in subgroups I-b and II-b (PPPD) - 3.8 times and 4.9 times, respectively. On this basis, it can be concluded that intestinal permeability was significantly increased with a statistically significant difference compared to the reference value ($p < 0.05$).

After 5 days, in patients after IL, intestinal permeability in PCS (subgroup I-a) decreased by 15.4%, and in PPPD (subgroup I-b) - by 19.8%. At the same time, in patients with PCS (subgroup II-a) who received standard treatment, excess intestinal permeability decreased by only 1%, and in case of PPPD (subgroup II-b), this figure continued to increase and after 5 days exceeded the initial value by 11.4%.

As a result of studying intestinal translocation, it was found that the concentration of endotoxin in the blood of patients with PPPD exceeded the norm by more than 10 times (Fig. 1). During IL and on the following days, a 2-fold decrease in this indicator was noted ($p<0.05$). The results obtained showed that intestinal lavage is accompanied by a significant drop in the level of endotoxin in the blood.

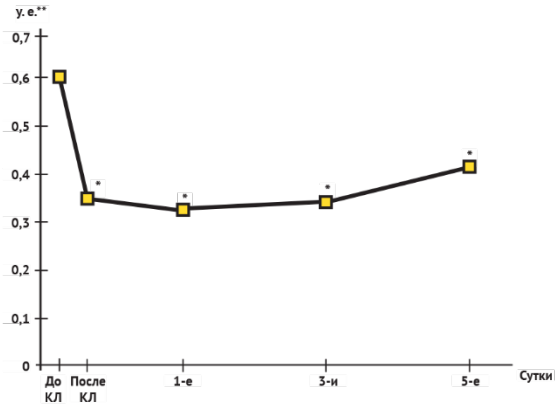

Fig. 1. Dynamics of endotoxin concentration in the blood of patients with combined poisoning by psychopharmacological drugs during intestinal lavage (n=23)
Notes: * — statistically significant difference from the original indicator ($p<0.01$, according to the Wilcoxon test); ** — normal values up to 0.06 EU/ml

The results of studying the effect of IL on the state of hematological intoxication indices in PPPD are presented in Table 4.

Table 4 shows that the initial levels of LII and NSI exceeded the norm by 6.3 and 2.4 times, respectively. After IL, there was an improvement in the integral indexes of intoxication (decrease in LII and NSI values by more than 52% and 70%, respectively), which indicated a decrease in the severity of endogenous intoxication.

Table 5 shows the dynamics of integral indexes of intoxication in the comparison group with severe PPPD.

Table 5

Dynamics of integral indexes of intoxication (LII and NSI) at the stages of examination of the comparison group of patients with severe combined poisoning by psychopharmacological drugs (n=50)

Research stages	Indexes			
	LII (norm 1.0±0.5 rel. units)	Δ,%	NSI (norm 0.06±0.02 rel. units)	Δ,%
Initial	6.1±1.1[1]	510	0,13±0,04[1]	117
After 1 day	7.4±1.6	640	0,18±0,05	200
After 3 days	5.2±0.8	420	0,17±0,07	183,3
After 5 days	3.5±0.4[2]	250	0,12±0,03	100

Notes: [1] — statistically significant difference between the initial indicator and the norm; [2] — statistically significant difference from the original indicator ($p<0.05$ according to Student's test); Δ,% — compared to the norm. NSI —neutrophil shift index; LII — leukocyte intoxication index

As can be seen from the table, the initial LII value in the group exceeded the norm by 6 times. Over the next 24 hours, this figure continued to grow. Only on the 3rd day did a tendency towards its decrease appear, and on the 5th day it became 1.7 times lower in relation to the initial state with a statistically significant difference in the indicators ($p < 0.05$). The initial value of the NSI in the comparison group exceeded the norm by more than 2 times. After one day, this indicator increased by 3 times, and then it began to decrease to the initial value by the 5th day.

Thus, in severe PPPD, the initially high values of integral indexes of intoxication significantly decreased by the time IL ended, while in case of standard treatment, similar dynamics were observed only by the 5th day.

Table 6 presents a comparative description of the incidence of pneumonia and mortality associated with it in the groups of patients.

Table 4

Dynamics of integral indexes of intoxication (LII and NSI) against the background of intestinal lavage in severe poisoning by psychopharmacological drugs (n=102)

Indexes	Norm	Indicator values before and after intestinal lavage			
		before IL	Δ,%[1]	after IL	Δ,%[2]
LII, rel. units	1.0±0.5	6.3±0.7[1]	530	3±0.6[2]	– 52.4
NSI, rel.units	0.06±0.02	0.143±0.03[1]	138,3	0.042±0.009[2]	– 70.6

Notes: [1] — statistically significant difference between the initial indicator and the norm; [2] — statistically significant difference from the original indicator ($p<0.05$ according to Student's test); Δ,%[1] — compared to the norm; Δ,%[2] — compared to the original indicator. NSI —neutrophil shift index; IL — intestinal lavage; LII — leukocyte intoxication index

Table 6

Incidence of pneumonia and mortality in the researched nosological forms in the study and comparison groups

Nosological form	Groups of patients	Number of patients	Incidence of pneumonia (abs.) %	p	Mortality in pneumonia (abs.) %	p
PPPD	Study Comparison	122 50	(32) 26,2 (27) 54,0	0,001*	(2) 6,25* (12) 44,4	0,000*
IMP	Study Comparison	330 245	(28) 8,5 (39) 15,9	0,006**	0 (2) 5,1	–
PCS	Study Comparison	170 155	(12) 7,1 (27) 17,4	0,006*	0 (2) 7,4	–
DT	Study Comparison	33 19	(3) 9,1 (17) 89,5	0,004*	0 (3) 17,6	–

Notes: * — statistically significant difference from the indicator of the comparison group ($p<0.05$ according to the Fisher exact probability criterion; ** — according to the χ^2 criterion. DT — delirium tremens; IMP — intravenous methadone poisoning; PPPD — poisoning by psychopharmacological drugs; PCS — poisoning by corrosive substances

It follows from the table that the inclusion of IL, which ensures total cleansing of the gastrointestinal tract, in the complex of treatment of the patients helps reduce the incidence of pneumonia in case of PPPD by 2.1; IMP – by 1.9; PCS – by 2.4 times, and DT – by 9.8 times. Differences in the incidence of pneumonia in the observed and corresponding comparison groups were statistically significant. It is noteworthy that in case of PPPD, the mortality rate in the observed group was more than 7 times lower than in the comparison group, with a statistically significant difference. As for PCS, IMP, and DT, there were no deaths from pneumonia in the observed groups of patients, while in the comparison groups the mortality rate from pneumonia was 5.1 (IMP), 7.4 (PCS) and 17.6% (DT).

DISCUSSION OF RESULTS

Pneumonia, as a complication of acute poisoning, develops in the period from several hours to 5–7 days after ingestion of poison [5].

Along with the generally accepted point of view on the etiopathogenesis of pneumonia as a complication of critical conditions, there exists a hypothesis according to which contamination of internal organs, including the lungs, can occur from the intestine due to increased permeability of its wall for pathogenic formations.

The digestive tract, being a link between the body and the external environment, performs not only digestive and transport, but also protective functions, and acts as a selective barrier to the flow of chemicals from the gastrointestinal tract into the internal environment. The ability to pass beneficial substances into the blood and lymph and block harmful ones is realized thanks to the complex anatomical and functional system of the intestinal barrier, the state of which is characterized by "physiological intestinal permeability". The "intestinal barrier" consists of three morphofunctional systems: preepithelial, epithelial and postepithelial barriers. An increase in the permeability of the intestinal wall means the transition of the mass exchange process from a physiological to a pathological state, in which massive translocation of microbial cells, their fragments and other pathological agents - PAMPs (pathogen-associated molecular structures: lipopolysaccharide (LPS), bacterial DNA and RNA, flagellin, lipoteichoic acid, lipopeptides, peptidoglycan, and (1→3)-β-D-glucan) from the intestine into the internal environment [29–32]. This phenomenon was named and is widely used in foreign literature as "leaky gut syndrome" [33]. R.D. Berg (1985) defined the translocation as the migration of viable bacteria from the gastrointestinal tract through the mucous membrane into the lymph and blood, and then into the internal organs of the macroorganism, for example, mesenteric lymph nodes, liver, spleen, etc. [34].

Intestinal barrier dysfunction is often reported in case of intestinal failure syndrome (IFS), as well as immunosuppressive states of the body [35, 36]. The key elements of IFS are gastrointestinal paresis and bacterial overgrowth syndrome (BOS) of opportunistic microflora against the background of the elimination of normal flora (bifidumbacteria and lactobacilli). The causes of IFS are multifactorial. Nonspecific factors include ischemia of the intestinal wall and hypoxia of epithelial cells with the formation of non-occlusive intestinal infarctions (NIIs) and damage to the

architectonics of the intestinal mucosa [37]. According to the literature, the pathogenesis of NIIs is associated with vasospasms, including those caused by iatrogenic hypercatecholemia, a decrease in perfusion pressure in the intestinal arterial system, hypovolemia and hemoconcentration [38, 39]. NIIs account for 44% of all vascular lesions of the intestine [23].

In places where epithelial cells are damaged, the mechanism of selective exchange of substances between the enteral and internal environments is disrupted, that is, the function of the pre- and epithelial barriers is impaired. In cases of immunodeficiency, the third (post-epithelial, or lymphocytic) barrier also fails, resulting in an uncontrolled by the macroorganism flow of PAMPs of "intestinal origin" into the lymph and blood. As a consequence, biologically active substances, including endotoxin of gram-negative bacteria, entering the bloodstream, trigger a systemic inflammatory response (SIR), which results in organ infectious and inflammatory processes with the subsequent development of multiple organ failure [16].

Under conditions of intestinal failure and changes in the intestinal microenvironment, shifts occur in the composition of the intestinal microbiota, which are characterized primarily by a decrease in the number of lactic acid bacteria and a simultaneous increase in the number of opportunistic and pathogenic microorganisms, which, by sending and perceiving signal molecules, are "able" to determine the size of their population [40]. When the number of opportunistic bacteria such as *Proteus*, *Escherichia coli*, *Klebsiella*, *Clostridia*, etc. reaches a certain value, their qualitative characteristics change: virulence and invasiveness increase by rearranging their genes [40]. Increased aggressiveness and expansiveness, on the one hand, and weakening of the intestinal barrier, on the other hand, allow pathogens to overcome the colonization resistance of the mucosal flora and break into the bloodstream of the portal vein. If they manage to overcome the next barrier in the form of liver macrophages, they enter the capillary network of the lungs, where they meet pulmonary macrophages.

The lungs, being one of the barriers in the intestine-systemic blood flow axis and acting as a physiological filter, naturally delay pathological substances on the path of their translocation from the intestine by the activation of pulmonary macrophages and a sharp increase in the pool of free radicals and pro-inflammatory cytokines – factors that cause damage and inflammation of lung tissue [39, 41]. The risk of developing such a process increases against the background of ventilation, hemodynamic and hemorheological disorders.

Figure 2 shows a diagram of the cause-and-effect relationship in the pathogenesis of pneumonia in critical conditions.

Fig. 2. Cause-and-effect relationships in the pathogenesis of pneumonia in critical conditions associated with exo- and endotoxicosis

Notes: OO — acute poisoning, CCC — cardiovascular system, ЖКТ — gastrointestinal tract, СИБР — bacterial overgrowth syndrome, СВР — systemic inflammatory response

The figure shows that among the causes influencing the development of pneumonia, there are such factors as: functional disorders of external respiration, circulatory system, and gastrointestinal tract (paresis and leaky gut syndrome). Based on this, it becomes apparent that to prevent pneumonia and resolve it, it is necessary to take into account all the factors contributing to its development.

It so happens that traditionally, in critical conditions, attention is first paid to eliminating disorders of vital systems - respiratory and cardiovascular, which is certainly justified. However, along with this, emergency medical measures to restore gastrointestinal tract functions in critical conditions have not yet become a generally accepted norm, much less a standard. On the one hand, this is due to the underestimation of the role of gastrointestinal disorders in the etiopathogenesis of pneumonia, and, on the other hand, until now there has been no available effective means of sanitation of the entire intestine. Long-term use of IL for AP proves its suitability as a remedy even in conditions of gastrointestinal paresis. The work by O.B. Lukyanets et al. (2022) presented the results of the effective resolution of IFS — restoration of the barrier function of the intestine, as well as digestive-transport, motor-evacuation processes of the gastrointestinal tract, and

normalization of microbiocenosis using IL in patients in chronic critical condition [42].

A multi-faceted research of the mechanisms of therapeutic effects of IL over many years has made it possible to establish that it causes a number of sanogenetic effects, of which the most significant, in the context of the topic under discussion, include the following: cleansing the intestinal cavity - removing a mass of toxicants and biologically active substances, that causes a decrease in the flow of PAMPs into the systemic circulation in the immediate period after IL (before the first meal); correction of water-electrolyte and acid-base imbalances, hemodilution, improvement of central hemodynamics and microcirculation [43]; restoration of the propulsive function of the gastrointestinal tract with the elimination of BOS, a decrease in the permeability of the intestinal wall and the flow of pathological agents into the systemic circulation in the postprandial period 5 days after IL.

Figure 3 shows a diagram of the sanogenetic mechanism of IL in the prevention and treatment of pneumonia.

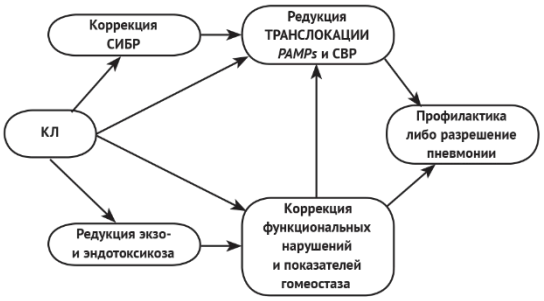

Fig. 3. Sanogenetic mechanism of intestinal lavage in the prevention and treatment of pneumonia as a complication of acute poisoning
Notes: КЛ — intestinal lavage, СИБР — bacterial overgrowth syndrome, СВР — systemic inflammatory response, PAMPs — Pathogen-associated molecular patterns

The figure shows that IL triggers a cascade of sanogenetic processes. First of all, these include eliminating the root cause of all disorders in the body - exotoxicosis. Of primary importance in this cascade is the cleansing of the intestines from toxicants and PAMPs, including LPS. We found that the initially high concentration of LPS in the blood of patients with PPPD sharply decreases after IL – by 52% of the initial level. Along with this, correction of microbiocenosis disorders occurs by eliminating opportunistic and pathogenic flora while simultaneously restoring the pool of normal flora by means of its mucosal part, the number of which increases after IL, which means its colonization resistance increases, blocking the growth and translocation of opportunistic flora. Elimination of endotoxin from the blood and its producer – opportunistic gram-negative flora – from the gastrointestinal tract as a result of IL most likely contributes to the reduction of SIR, and, consequently, lowering the risk of developing pneumonia.

CONCLUSION

Our own observations and analysis of literary sources showed that in various nosological forms of acute poisoning, the most common complication is pneumonia. We found that despite the difference in the chemical nature and characteristics of such nosological forms of poisoning as PPPD and PCS, their common manifestation was intestinal dysbiosis and increased permeability of the intestinal wall above normal. At the same time, endotoxin of gram-negative bacteria was found in the blood (of patients with PPPD) in a concentration ten times higher than the norm. These processes were accompanied by an increase in hematological intoxication indices.

Under these conditions, the use of IL contributed to the elimination of intestinal dysbiosis by removing regional microflora together with opportunistic flora from the gastrointestinal tract, reduction of pathological permeability of the intestinal barrier, and a sharp decrease in the concentration of endotoxin in the blood and hematological intoxication indices. There is an associative connection between these processes, as well as with the fact of a decrease in the incidence of pneumonia and the severity of its course. It is noteworthy that in patients of the comparison groups, we did not observe such pronounced positive changes in the studied indicators, the differences of which in the study and comparison groups were statistically significant. Thus, we can conclude that the development of pneumonia during poisoning has a close connection with functional disorders of the gastrointestinal tract, and IL interrupts this connection and, as a result, ensures the prevention or resolution of pneumonia.

By this research, the authors hope to attract the attention of the scientific community to the emergence of a new paradigm in the pathogenesis of infectious and inflammatory complications of acute poisoning and accompanying endotoxicosis. Looking at the problem from a new perspective allows us to effectively prevent and combat this kind of complications.

FINDINGS

1. In case of poisoning by psychopharmacological drugs and corrosive substances, intestinal dysbiosis develops in the form of a decrease in the population of lactic acid bacteria by 1–2 orders and an increase in opportunistic flora over 105 CFU. As a result of intestinal lavage, the normal number of intestinal microflora is restored: the proportion of patients with poisoning by corrosive substances with an initially reduced titer of fecal bifidobacteria and lactobacilli decreases on the 5th day after intestinal lavage by 3.5 and 2 times, respectively; whereas in the comparison group for the same period, these indicators are only 1.5 and 1.2 times lower compared to the initial values. The proportion of patients with poisoning by psychopharmacological drugs, who have an initially reduced titer of bifidobacteria and lactobacilli, decreases by 3 times on the 5th day after intestinal lavage with a statistically significant difference in indicators ($p < 0.05$). In the comparison group for the same period, these same indicators are only 1.2 and 1.3 times lower compared to the initial values.

2. Poisoning by psychopharmacological drugs and corrosive substances is accompanied by a pathological statistically significant ($p < 0.05$) increase in the permeability of the intestinal barrier by 3.8–4.9 and 4.3–4.4 times, respectively. Intestinal lavage provides effective cleansing of the gastrointestinal tract (to clean rinsing water) and helps reduce excessive permeability of the intestinal barrier by 1.2 times (poisoning by corrosive substances) and 1.25 times (poisoning by psychopharmacological drugs). While in the comparison group, in case of poisoning by psychopharmacological drugs, intestinal permeability continues to increase over the next 5 days and exceeds the initial value by 11.4%.

3. In case of poisoning by psychopharmacological drugs, a tenfold excess of the reference value of the endotoxin of gram-negative bacteria in the blood is registered; at the same time, there is an increase in the leukocyte intoxication index by 6, and the neutrophil shift index by 2 times. As a result of intestinal lavage, the initially high level of endotoxin in the blood decreases by 2 times, while there is a decrease in the leukocyte intoxication index and neutrophil shift index by 2.1 and 3.4 times, respectively, with a statistically significant difference from the initial indicator ($p < 0.05$).

4. In the groups of patients who underwent intestinal lavage, there is a decrease in the incidence of pneumonia from 1.9 to 9.8 times, and the risk of death from pneumonia by 7 times in case of severe poisoning by psychopharmacological drugs, and in case of poisoning by corrosive substances and methadone, as well as delirium tremens - to zero. Differences in indicators in the observed and corresponding comparison groups are statistically significant ($p<0.05$).

REFERENCES

1. Luzhnikov EA, Kostomarova LG. Ostrye otravleniya. Moscow: Meditsina Publ.; 2000. (In Russ.)
2. Lodyagin AN, Livanov GA, Nikolayeva IP, Batotsyrenov BV, Shestova GV, Fedicheva NS, et al. Acute Respiratory Failure in Acute Poisoning by Neutrotropic Substances. *General Reanimatology*. 2008;4(3):30. (In Russ.) https://doi.org/10.15360/1813-9779-2008-3-30
3. Livanov GA, Shestova GV, Batotsyrenov BV, Lodyagin AN, Ivanova TM, Sizova KV. Role of Pulmonary Hyperhydration in Pathogenesis of Acute Lung Injury in Heavy Poisoning by Neurotropic Agents. *Extreme medicine.* 2011;(3):92–99. (In Russ.)
4. Il'yashenko KK, Luzhnikov EA. *Toksicheskoe porazhenie dykhatel'noy sistemy pri ostrykh otravleniyakh*. Moscow: Medpraktika–M Publ.; 2004. (In Russ.)
5. Iskandarov AI. A toxicometric assessment of pneumonias and acute respiratory failure in poisonings. *Sud Med Ekspert*. 1993;36(3):23–25. PMID: 8378975. (In Russ.)
6. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol*. 2000;21(8):510–515. PMID:10968716 https://doi.org/10.1086/501795
7. Gel'fand BR, Gologorskiĭ VA, Belotserkovskiĭ BZ, Gel'fand EB, Alekseeva EA, Nikol'skiĭ VE. Nosocomial pneumonia in intensive care units (review of the literature). *Anesteziol Reanimatol*. 1999;(3):38–46. (In Russ.)
8. Maev IV, Busarov GA, Andreev NG. Gospital'nye pnevmonii. Moscow; 2002. (In Russ.)
9. *Meditsinskiy spravochnik bolezney. Bolezni organov dykhaniya*. Pnevmoniya. Available at: https://www.krasotaimedicina.ru/diseases/zabolevanija_pulmonology/pneumonia [Accessed May 13, 2024]
10. Batotsyrenov BV, Livanov GA, Martynova YeI, Lodyagin AN, Antonevich YeV, Shestova GV. Correction of Immunological Disorders in Acute Pneumonia-Complicated Intoxications. *General Reanimatology*. 2007;3(3):81. (In Russ.) https://doi.org/10.15360/1813-9779-2007-3-81
11. Bezanson JL, Kinney M. Analysis of factors related to the development of ventilator-associated pneumonia: use of existing databases. *Am J Crit Care*. 2001;10(1):68. PMID: 11153188
12. Parakhonskiy AP. Narusheniya immunnoy sistemy u bol'nykh pnevmoniey i metody ikh korrektsii. *Modern high technologies*. 2005;(1):116–117. (In Russ.)
13. Karaulov AV. Immunologiya vnebol'nichnykh pnevmoniy. In: Chuchalin AG, Sinopal'nikov AI, Chernekhovskaya NE. *Pnevmoniya*. Moscow: Ekonomika i informatika Publ.; 2002: 67–92. (In Russ.)
14. Protsenko DN, Gel'fand BR, Yakovlev SV, Ramishvili VSh. Faktory riska razvitiya i neblagopriyatnogo iskhoda nozokomial'noy pnevmonii, svyazannoy s iskusstvennoy ventilyatsiey legkikh, u bol'nykh tyazheloy travmoy. *Infektsii i antimikrobnaya terapiya*. 2002;(4):143–146 (In Russ.)
15. *Tolstokishechnaya detoksikatsiya i metabolicheskaya korrektsiya*. Saint Petersburg: Izd-vo SPb MAPO Publ.; 1995. (In Russ.)

16. Savel'ev VS (ed.) *Sindrom kishechnoy nedostatochnosti v ekstrennoy khirurgii organov bryushnoy polosti: usovershenstvovannaya meditsinskaya tekhnologiya.* Moscow: MAKS Press; 2006. (In Russ.)
17. Hartl WH, Jauch KW. [Abdominal infection: surgical domain]. *Chirurg*. 2006;Suppl:33–34. PMID: 16802425
18. Mikhailova ZF, Lazebnik LB, Parfenov AI. [Bronchopulmonary lesions in chronic inflammatory bowel diseases]. *Ter Arkh*. 2010;82(3):61–64. PMID: 20564926 (In Russ.)
19. Kostyuchenko AL, Kostin ED, Kurygin AA. *Enteral'noe iskusstvennoe pitanie v intensivnoy meditsine*. Saint Petersburg: Spetsial'naya literature Publ.;1996. (In Russ.)
20. Beloborodova NV. Integration of Metabolism in Man and His Microbiome in Critical Conditions. *General Reanimatology*. 2012;8(4):42. (In Russ.) https://doi.org/10.15360/1813-9779-2012-4-42
21. *Lipopolisakharidy gramotritsatel'nykh bakteriy.* (In Russ.) Available at: http://propionix.ru/lipopolisaharidy-gramotricatelnyh-bakterij [Accessed May 13, 2024]
22. Oparina ON. Biological Properties of the Endotoxin Derived from Gram-Negative Intestinal Bacteria. *Modern scientific researches and innovations.* 2014;(1). (In Russ.) Available at: https://web.snauka.ru/issues/2014/01/31034?ysclid=llc7bnwdcy907849452 [Accessed May 13, 2024]
23. Zimina LN, Mikhailova GV, Barinova MV, Pavlenko YeYu, Polozov MA, Popov SV, et al. Morphological Aspects of Acute Intoxication With Azaleptin. *Forensic Medical Expertise*. 2008;(3):8–10. (In Russ.)
24. Leyderman IN, Sentsov VG, Vorontsov SV. Fenomen povyshennoy kishechnoy pronitsaemosti kak proyavlenie sindroma kishechnoy nedostatochnosti (SKN) u bol'nykh s otravleniyami prizhigayushchimi zhidkostyami sredney i tyazheloy stepeni. *Intensivnaya terapiya*. 2008;(2). (In Russ.) Available at: http://icj.ru/journal/number-2-2008/158-fenomen-povyshennoy-kishechnoy-pronicaemosti-kak-proyavlenie-sindroma-kishechnoy-nedostatochnosti-skn-u-bolnyh-s-otravleniyami-prizhigayuschimi-zhidkostyami-sredney-i-tyazheloy-stepeni.html [Accessed May 13, 2024]
25. *Delirium rating scale–R–98 (DRS-R-98)*. Available at: https://dementiaresearch.org.au/wp-content/uploads/2016/06/DRS-R-98-Form.pdf [Accessed May 13, 2024]
26. *Otraslevoy standart OST 91500.11.0004-2003 "Protokol vedeniya bol'nykh. Disbakterioz kishechnika". Prikaz Minzdrava RF ot 9 iyunya 2003 g. No 231.* (In Russ.) Available at: https://base.garant.ru/4179500/?ysclid=llc3gwssab161762958 [Accessed May 13, 2024]
27. Johnston SD, Smye M, Watson RG, McMillan SA, Trimble ER, Love AH. Lactulose-mannitol intestinal permeability test: a useful screening test for adult coeliac disease. *Ann Clin Biochem*. 2000;37(Pt 4):512–519. PMID: 10902869 https://doi.org/10.1177/000456320003700413
28. Evdokimova NV, Spiridonova TG, Chernen'kaya TV. Lipopolisakharidy (endotoksiny) gramotritsatel'nykh bakteriy kak markery bakteriemii I septicheskogo sostoyaniya u patsientov s ozhogami. *Meditsina kriticheskikh sostoyaniy.* 2009; 5: 47–51. (In Russ.)
29. Silva-Gomes S, Decout A, Nigou J. Pathogen-Associated Molecular Patterns (PAMPs). In: Parnham MJ. (ed.) *Compendium of Inflammatory Diseases*. Birkhäuser Basel; 2020. Available at: https://link.springer.com/referenceworkentry/10.1007/978-3-0348-0620-6_35-1 [Accessed May 13, 2024]
30. Nikitenko VI, Zakharov VV, Borodin AV, Simonenko EV, Kopylov VA, Fomina MV. Rol' translokatsii bakteriy v patogeneze khirurgicheskoy infektsii. *Pirogov Russian Journal of Surgery.* 2001;(2):63–66. (In Russ.)
31. Tret'yakov EV, Varganov MV, Nifontova EE. Sovremennyy vzglyad na kishechnuyu translokatsiyu bakteriy kak osnovnuyu prichinu gnoyno-septicheskikh oslozhneniy pri destruktivnom pankreatite. *Advances in current natural sciences*. 2013;(9):78–80. (In Russ.)
32. Trukhan DI, Chusova NA. Syndrome of Increased Epithelial Permeability of the Intestine in Real Clinical Practice. *Therapy*. 2020;(8):174–185. (In Russ.) https://doi.org/10.18565/therapy.2020.8.174-185
33. Usuda H, Okamoto T, Wada K. Leaky Gut: Effect of Dietary Fiber and Fats on Microbiome and Intestinal Barrier/ Haruki Usuda, Takayuki Okamoto and Koichiro Wada. *Int J Mol Sci*. 2021;22(14):7613. PMID:34299233 https://doi.org/10.3390/ijms22147613
34. Berg RD. Bacterial translocation from the intestines. *Jikken Dobutsu*. 1985;34(1):1–16. PMID: 3987819 https://doi.org/10.1538/expanim1978.34.1_1
35. Ermolov AS, Popova TS, Pakhomova GV, Uteshev NS. *Sindrom kishechnoy nedostatochnosti v neotlozhnoy abdominal'noy khirurgii (ot teorii k praktike)*. Moscow: MedEkspert-Press Publ.; 2005. (In Russ.)
36. Dremina NN, Chepurnykh EE, Fadeeva TV, Shurygina IA. Bacterial Translocation in Peritonitis. *Modern Problems of Science and Education*. 2018;(6). Available at: https://science-education.ru/ru/article/view?id=28251 [Accessed May 13, 2024].
37. Nault JC, Mégarbane B, Théodore J, Deye N, Nemeth J, Valleur P, et al. Poisoning-related bowel infarction: Characteristics and outcomes. *Clin Toxicol (Phila)*. 2009;47(5):412–418. PMID: 19492932 https://doi.org/10.1080/15563650902922607
38. Küçükaydin M, Kocaoğlu C, Köksal F, Kontaş O. Detection of intestinal bacterial translocation in subclinical ischemia-reperfusion using the polymerase chain reaction technique. *J Pediatr Surg*. 2000;35(1):41–43. PMID: 10646771 https://doi.org/10.1016/s0022-3468(00)80010-x
39. Miyashita M, Onda M, Matsuda T, Moriyama Y, Takizawa T, Kim DY, et al. [Endotoxin-induced lung injury – the role of leukocytes and oxidants]. *Kokyu To Junkan*. 1989;37(1):65–70. (In Jap.) PMID: 2734494.
40. Shenderov BA. *Meditsinskaya mikrobnaya ekologiya i funktsional'noe pitanie: in 3 vol.* Vol. I: Mikroflora cheloveka i zhivotnykh i ee funktsii. Moscow: GRANT""; 1998. (In Russ.)
41. Souza AL Jr, Poggetti RS, Fontes B, Birolini D. Gut ischemia/reperfusion activates lung macrophages for tumor necrosis factor and hydrogen peroxide production. *J Trauma*. 2000;49(2):232–236. PMID: 10963533 https://doi.org/10.1097/00005373-200008000-00008
42. Lukyanets OB, Petrova MV, Yakovleva AV, Shestopalov AE. Role of intestinal lavage in the normalization of the functions of the gastrointestinal tract in patients with chronic critical illness. *Clinical nutrition and metabolism*. 2022;3(3):132–139. (In Russ.) https://doi.org/10.17816/clinutr111148
43. Matkevich VA, Potskhveriya MM, Simonova AYu, Sukhodolova GN, Belova MV, Bitkova EE. Management of Disorders of Homeostasis with Saline Enteral Solution in Acute Poisoning with Psychopharmacological Drugs. *Russian Sklifosovsky Journal Emergency Medical Care*. 2020;9(4):551–563. https://doi.org/10.23934/2223-9022-2020-9-4-551-563

Received on 03/10/2023
Review completed on 15/10/2023
Accepted on 26/03/2024