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## GENDER AND ETIOLOGICAL FEATURES OF MODERN SALMONELLOSIS

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### Summary

The main clinical and epidemiologic features of modern salmonellosis in acute disease period were analyzed. The studied integrative indices of endogenous intoxication in groups indicate disturbances in the immune system, such as the prevalence of humoral and depression of cellular components of immune system, development of endogenous intoxication due to body autointoxication by destruction of own cells and by influence of bacterial endo- and exotoxins, evident inflammatory reaction. In the acute phase reactions of delayed type prevail over hypersensitivity of immediate type that causes to launching allergic mechanisms on the background of intoxication.

**Keywords:** salmonellosis, clinical picture, integral indicators, integrative indicators, endogenous intoxication.

# ГЕНДЕРНІ ТА ЕТІОЛОГІЧНІ ОСОБЛИВОСТІ СУЧАСНОГО САЛЬМОНЕЛЬОЗУ

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## Резюме

Проаналізовано основні клінічні та епідеміологічні ознаки сучасного сальмонельозу в гострий період захворювання. Дослідженні інтегративні показники ендогенної інтоксикації у групах вказують на порушення в імунній системі, а саме превалювання гуморальної і пригнічення клітинної ланок імунітету, розвиток ендогенної інтоксикації внаслідок автоінтоксикації організму при деструкції власних клітин та при дії бактеріальних ендо- та екзотоксинів, виразну запальну реакцію. У гострому періоді спостерігається переважання реакцій уповільненого типу над гіперчутливістю негайного типу, що призводить до запуску алергічних механізмів на тлі інтоксикації.

**Ключові слова:** сальмонельоз, клініка, інтегральні показники, інтегративні показники, ендогенна інтоксикація.

# ГЕНДЕРНЫЕ И ЭТИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ СОВРЕМЕННОГО САЛЬМОНЕЛЛЕЗА

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## Резюме

Проведен анализ основных клинических и эпидемиологических особенностей течения сальмонеллеза в острый период заболевания и выявлены гематологические изменения. Исследованные интегративные показатели эндогенной интоксикации в группах указывают на нарушения в иммунной системе, а именно превалирование гуморального и угнетение клеточного звеньев иммунитета, развитие эндогенной интоксикации вследствие аутоинтоксикации организма при деструкции собственных клеток и при действии бактериальных эндо- и экзотоксинов, выраженную воспалительную реакцию. В остром периоде наблюдается преобладание реакций замедленного типа над гиперчувствительностью немедленного типа, что приводит к запуску аллергических механизмов на фоне интоксикации.

**Ключевые слова:** сальмонеллез, клиника, интегральные показатели, интегративные показатели, эндогенная интоксикация.

## Introduction

Salmonellosis is a widespread intestinal infection. Epidemic breakouts are observed almost in all regions of the world. This disease is of relevance also for Ukraine, especially now, under the conditions of fall of economic and social living standards [1 - 4].

By disturbance of metabolic processes toxins of endogenous and exogenous origin are accumulated in cells that predetermines clinical and laboratory changes – endogenous intoxication syndrome (EIS) [5, 6]. In clinical picture of salmonellosis, dehydration syndrome together with EIS predetermines severity of disease course and its prognosis [7].

The following kinds of markers are mostly used for EIS index evaluation in clinical characteristics of illness: integral – evaluation of overall condition (temperature rise, intensity of adynamia, apathy, sleepiness, irritancy, decreased appetite, weight loss, pain of any

location, determination of central hemodynamics indicators) and immunological – (calculation of integrative indicators of endogenous intoxication) [6].

**Objective of the paper.** To study peculiarities of clinical characteristics, epidemiology, changes of integral, integrative indicators of endogenous intoxication, immunoreactivity in acute period of salmonellosis.

### **Patients and methods**

During 2012 – 2016 189 patients with salmonellosis, which underwent medical treatment in Sumy regional clinical infectious hospital named after Z. Y. Krasovytskoho, were examined. They were taken to hospital at  $(2.26 \pm 0.08)$  day. All diagnostic and treatment procedures were carried out at patients' informed consent. Criteria for enrolling were: clinical and anamnestic (hospitalization not later than 72 hours from illness onset; presence of typical clinical features of salmonellosis of moderate course – acute onset, intoxication, pain, diarrhea, dehydration); data of epidemiological anamnesis (consumption of food of low or doubtful quality, with insufficient heat treatment, breakout etc); laboratory (bacteriological examination of stomach washing waters and / or vomiting matters and / or salmonella feces).

Criteria for excluding from the investigation were: clinical and anamnestic (hospitalization later than 72 hours from illness onset; mild or severe course of salmonellosis; presence of co-morbidity of gastro-intestinal tract and hepatobiliary system; chronic diseases of cardiovascular, urinary, endocrine system at the stage of decompensation); laboratory (negative results of bacteriological examination).

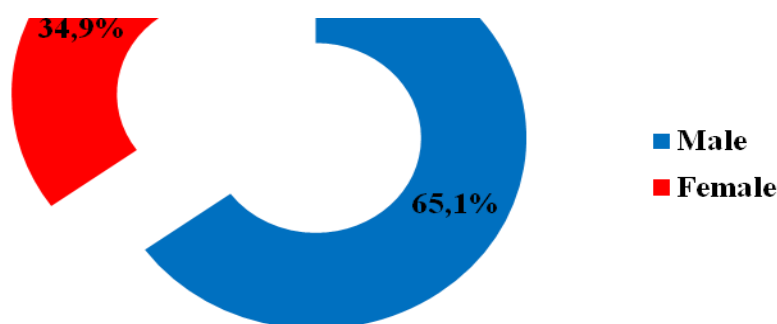
The following was carried out: anamnestic data collection; clinical laboratory examinations: clinical blood analysis (analyzer Cobas Micros), bacteriological feces examination, as well as integrative endogenous intoxication and immunoreactivity indicators were calculated: leucocyte intoxication index (LII), hematological index of intoxication (HII), index of leukocytes shift (ISL), Krebs index (KI), immunoreactivity index (IR), lymphocytic-granulocytic index (ILG), neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), neutrophil reactive response (NRR), index of leukocyte and ESR ratio (ILES), lymphocyte index ( $I_{lymph}$ ), eosinophils-lymphocytes ratio (ELR), index of allergization (IA), nuclear index (NI), index of intoxication severity (IIS) [8].

The group contained 44 clinic anamnestic healthy blood donors from Sumy regional centre of blood supply service and transfusiology aged  $(37.95 \pm 1.72)$  years old. Sex composition of this group was equal – 22 men and women each.

All data were entered into “Electronic card of investigation”. The results of clinical observation and carried out investigations were processed using method of variation statistics (Student’s t-test, Pearson's chi-squared test) using software Microsoft Office Excel 2010, Statistica 10 and on-line calculator (<http://medstatistic.ru/calculators/calchit.html>).

### Results of the investigation and its discussion

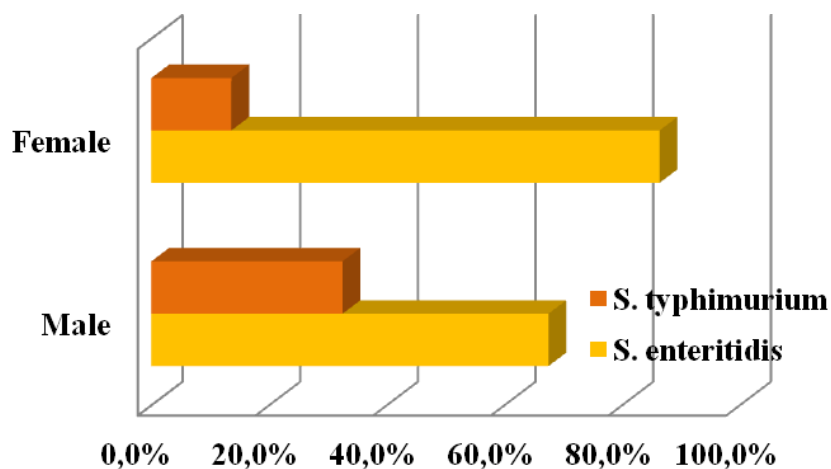
Men prevailed among the examined patients with salmonellosis: 123 persons, 65.1 % ( $p < 0.01$ ) (Fig. 1).



**Figure 1 – Sex distribution of the examined patients**

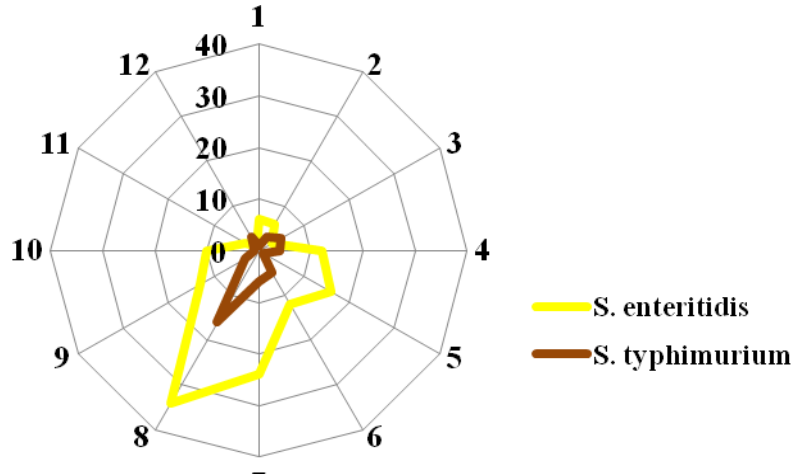
Patients’ age didn’t depend on sex and was: ( $43.29 \pm 1.46$ ) years old in men and ( $43.12 \pm 2.20$ ) years old in women.

Causative factor was predominantly *S. enteritidis* (140 persons, 74.10 %), *S. typhimurium* was three times more rarely manifested (49, 25.90 %) ( $p < 0.01$ ). *S. enteritidis* caused the illness more rarely in women than in men ( $p < 0.01$ ) (Fig. 2).



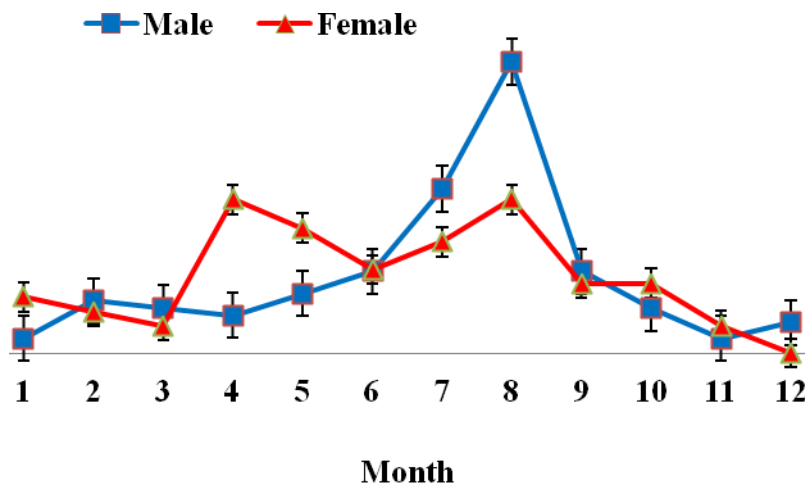
**Figure 2 – Etiological structure of salmonellosis depending on age**

Little number of patients with salmonellosis was taken to hospital in August with growth beginning in May – June. It has been established that by diseases caused by *S. enteritidis* admission to hospital is greater during the whole year with raise in April – September and by *S. typhimurium* it is more often in June – September (Fig. 3).



**Figure 3 – Dependence of periodicity of patients with salmonellosis on etiology**

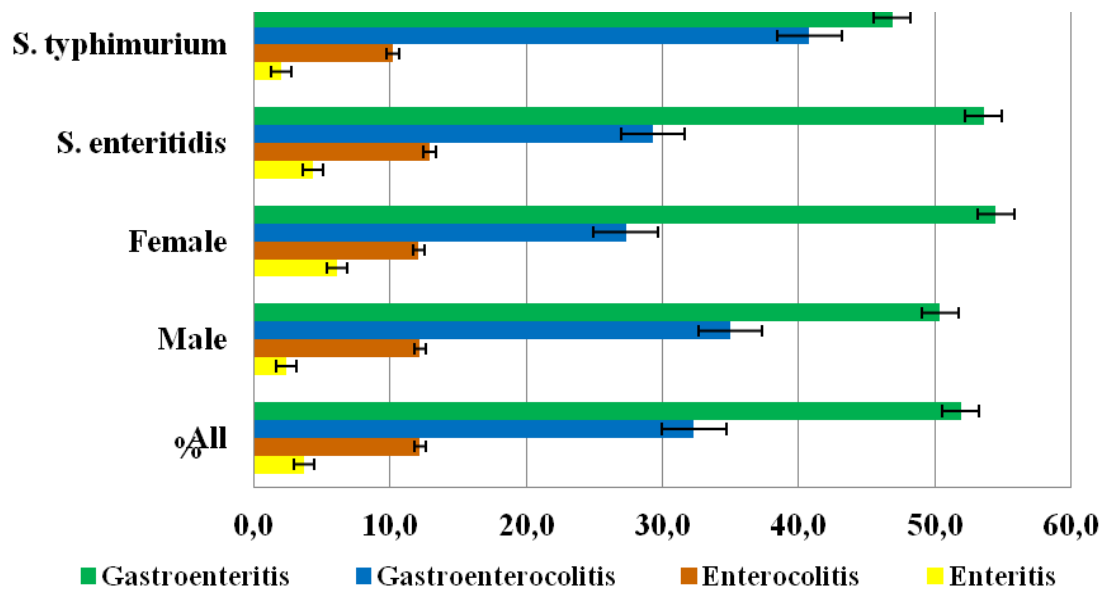
Women were taken to hospital more intensively in April – August with even hospitalization (9.10 % to 16.70 % monthly), as far as men sought medical advice more intensively in June – September with maximum hospitalization in June (17.90 %) and August (31.70 %) (Fig. 4).



**Figure 4 – Dependence of hospitalization periodicity of patients with salmonellosis on age**

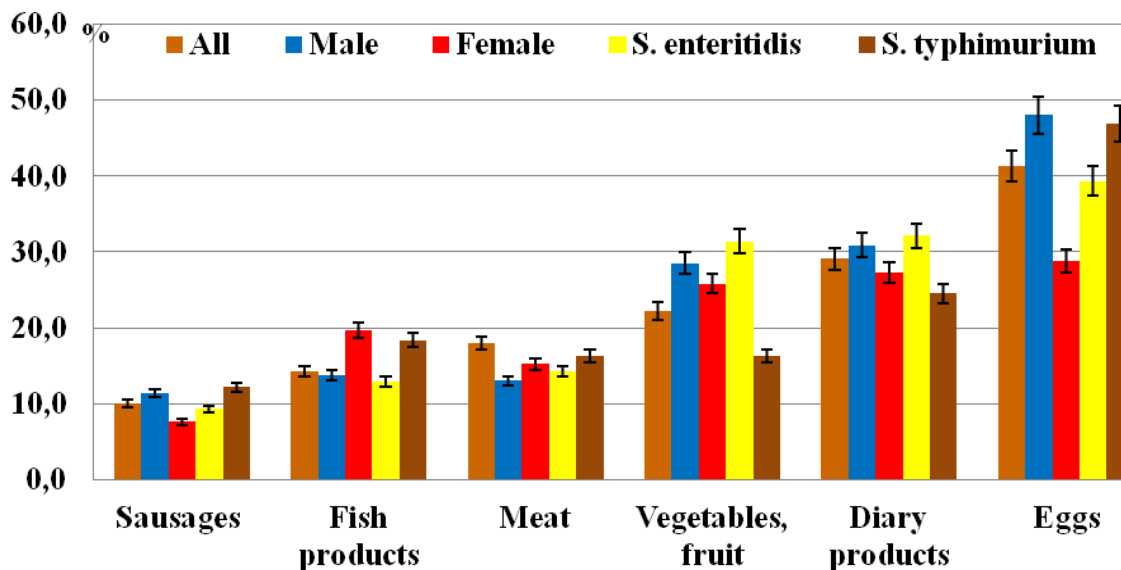
While analyzing periods of seeking medical advice from the moment of disease onset, it has been established that all patients were taken to hospital on the second-third day not depending on sex (men - (2.32±0.10) days; women - (2.15±0.13) days) and etiology (S. enteritidis - (2.20±0.08) days; S. typhimurium - (2.43±0.17) days) (p>0.05).

While studying clinical disease variants in general, it has been established that gastroenteritic variant prevails in all patients irrespective of gender, the second by frequency is gastroenterocolitic (more rarely in women, p<0.05), the third is enterocolitic variant, enteric one was observed more rarely (prevailing in women p<0.01). By salmonellosis caused by S. enteritidis, no differences in distribution of clinical variants of previous rates were defined. Whereas, by the diseases caused by S. typhimurium gastroenterocolitic and gastroenteritic were registered with the same frequency (Fig. 5).



**Figure 5 – Patient distribution by clinical disease forms**

In majority of cases patients with salmonellosis connected their disease with several probable transmission factors, the most popular are poultry eggs (prevailed in men), dairy products, meat – and fish products (prevailed in women), vegetables and fruit etc. By salmonellosis caused by S. typhimurium transmission factors more often than by S. enteritidis were eggs, meat, fish products, sausages; by S. enteritidis were dairy products, vegetables and fruit (p<0.05) (Fig. 6).



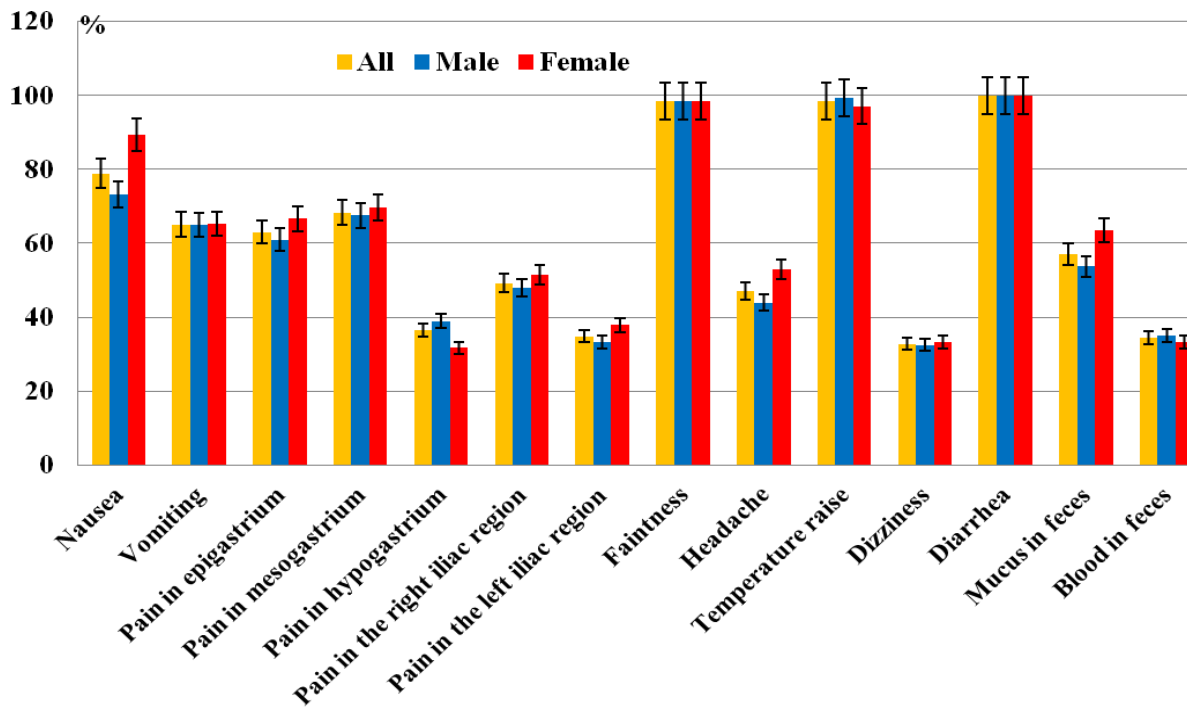
**Figure 6 – Probable transfer factors by salmonellosis**

By hospitalization almost all patients had complaints of: weakness, temperature raise and diarrhea. Nausea (78.84%) and vomiting (65.08 %) ( $p < 0.01$ ) were the second among complaints. Stool frequency varied within the range ( $9.10 \pm 0.43$ ) times a day, vomiting - ( $2.30 \pm 0.20$ ) times a day. All patients complained of pain in different abdominal areas. It occurred in several areas simultaneously: most frequently in mesogastric (68.25 %) and epigastric areas (62.96 %); more rarely – in the right iliac region (49.21 %), in hypogastrium (36.51 %) and the left iliac region (34.92%). Headache was anamnestically registered by 47.09% patients with salmonellosis, dizziness – 32.80%. Additions of mucus in feces were noted by half of patients (57.14%), blood in feces was 1.66 more rarely found (34.39 %) ( $p < 0.01$ ) (Fig. 7).

Comparing symptom severity by gender characteristic, predominance of the following complaints has been identified: in women – of nausea, pain in epigastric and the left iliac region, headache, additions of mucus in feces ( $p < 0.05$ ); in men – of pain in hypogastrium ( $p < 0.05$ ) (Fig. 7).

Dehydration (96.30 %) and abdominal pain by palpation (95.80 %) were the most popular symptoms by physical examination ( $p < 0.01$ ) (Fig. 8). In majority of patients pain by palpation was localized in several regions simultaneously, but the most frequently in mesogastrium (74.60 %) and in epigastrium (71.43 %). More rarely it was in the right iliac region (60.85 %) ( $p < 0.01$ ). More rarely pain was localized in hypogastrium (32.80%) and the left iliac region (34.39 %) ( $p < 0.01$ ). Increased bowel sounds were detected in considerable part of the examined by palpation (73.02%). Spasm of sigmoid colon was observed in little number of patients (13.23 %).





**Figure 7 – Complaint severity in examined persons by hospitalization**

Dependence of objective symptoms on gender and etiology has been determined. In such a way, increase in liver sizes, pain in hypogastrium (35.77 % - in men, 27.27 % - women) and spasm of sigmoid colon (17.07 % - men, 6.06 % - women) were detected more often in men ( $p < 0.05$ ). By salmonellosis caused by *S. typhimurium* pain syndrome was localized in mesogastrium (83.67 % - *S. typhimurium*, 71.43 % - *S. enteritidis*) and hypogastrium (38.78 % - *S. typhimurium*, 30.17 % - *S. enteritidis*), whereas it was met more rarely in the right iliac region (53.06 % - *S. typhimurium*, 63.57 % - *S. enteritidis*) ( $p < 0.05$ ) (Fig. 8).

Increase in liver sizes was in every second-third patient (38.19 %), in average in  $(1.85 \pm 0.08)$  cm. Its sizes were changed more significantly and often in men (43.09 % - men, 28.79 % - women) ( $p < 0.05$ ) (Fig. 9).

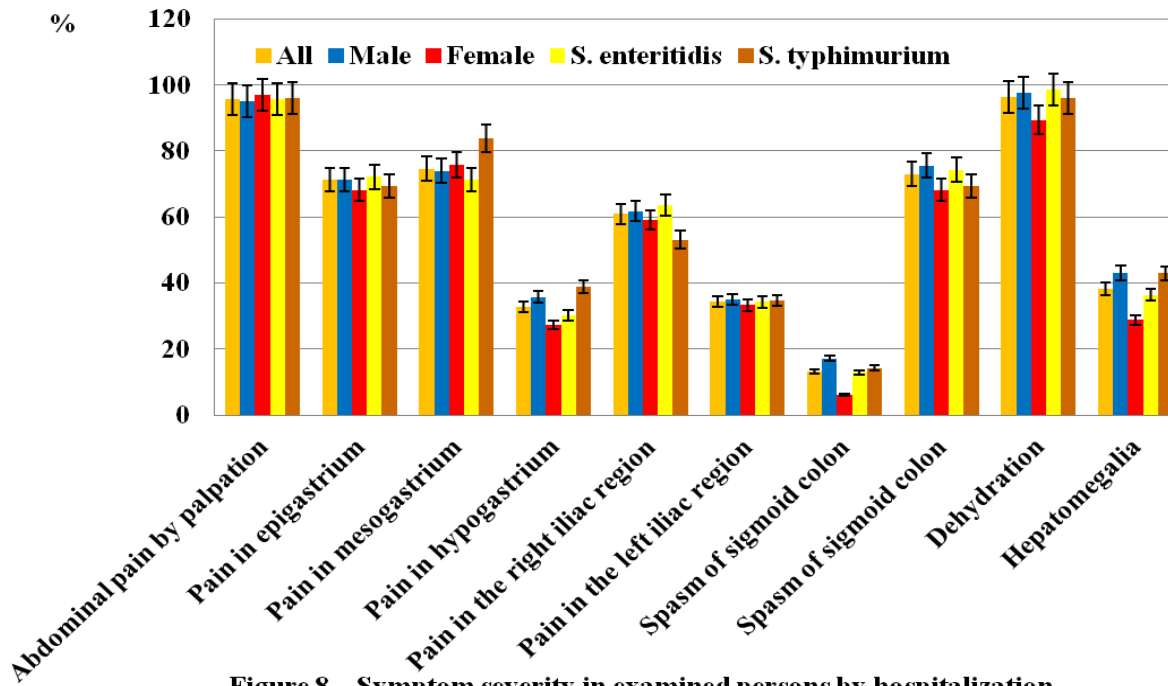


Figure 8 – Symptom severity in examined persons by hospitalization

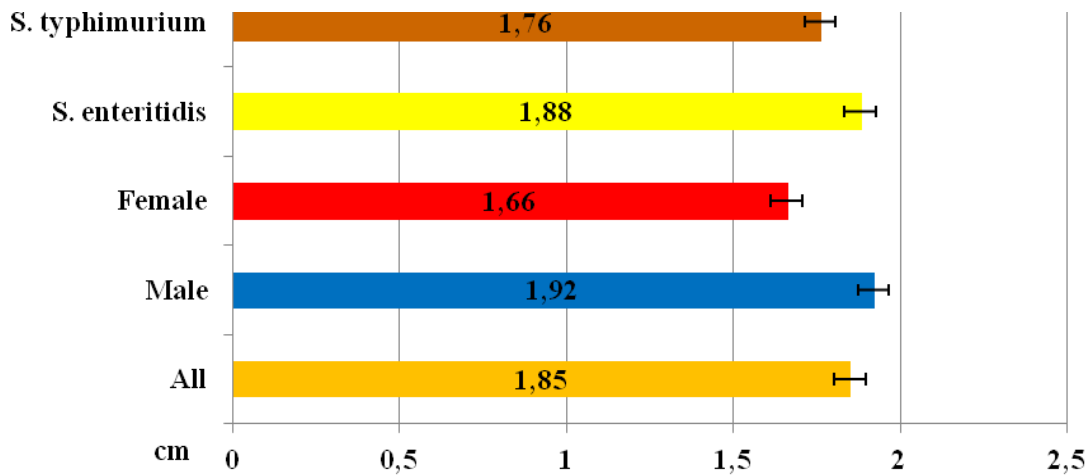


Figure 9 – Increase in liver sizes in patients with salmonellosis

Temperature increase was recorded in all patients (95.77%). It should be noted that in the first day of illness at pre-hospitalization stage temperature increase was more intensive ( $38.54 \pm 0.06$ ) °C, compared with hospitalization - ( $37.88 \pm 0.07$ ) °C ( $p < 0.01$ ), at the same time dependence of its changes on gender and etiology was absent (Fig. 10).

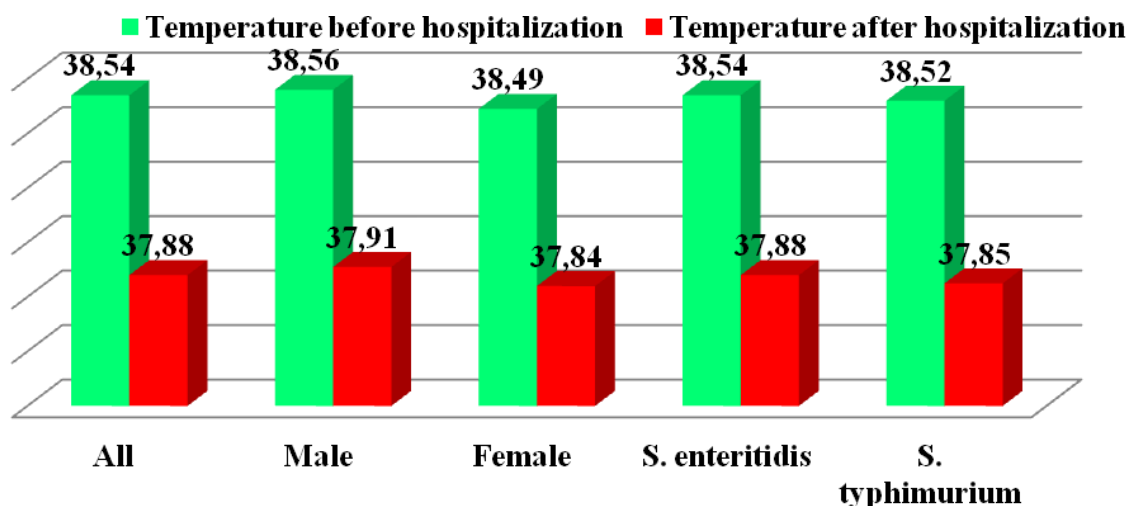


Figure 10 – Temperature increase in patients with salmonellosis (°C)

Diarrhea was discovered in all patients up to  $(9.10 \pm 0.43)$  times a day. Herewith, tendency to increase of this symptom in women was observed (women -  $(9.70 \pm 0.85)$  times a day, men -  $(8.95 \pm 0.50)$  times a day) and by salmonellosis caused by *S. enteritidis* (*S. enteritidis* -  $(9.54 \pm 0.53)$  times a day, *S. typhimurium* -  $(8.28 \pm 0.78)$  times a day) (Fig. 11).

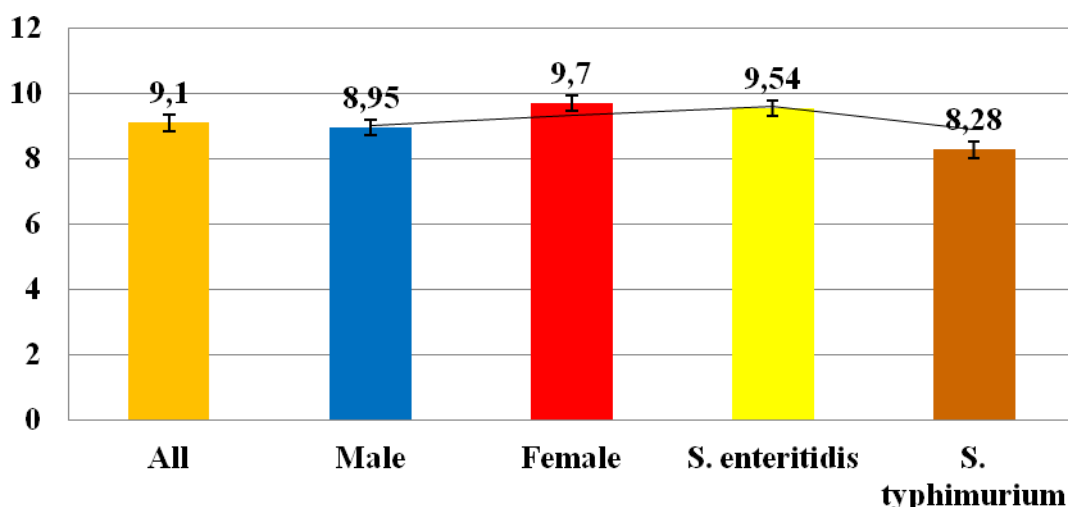


Figure 11 – Stool frequency in patients with salmonellosis in the period of manifest (times a day)

Based in findings of clinical blood analysis in the examined patients of various groups in acute period of disease, integrative hematological indexes were calculated and their statistic processing was carried out for EIS and immunoreactivity evaluation. It has been established that LII, ISL, HII, IIS, NRR, NLR, ILESR, NI indicators increased and ILG,  $I_{lymph}$ , ELR, IA indexes reduced. There were no authentic changes of IR and LMR, although tendency to its reduction was observed during salmonellosis caused by *S. typhimurium* ( $t = 1.64$  и  $1.60$  correspondingly, at  $t=1.98$   $p=0.05$ ) (table1).

Table 1 – Integrative indicators of endogenous intoxication and immunoreactivity in patients with salmonellosis by hospitalization depending on etiology (M±m)

Rate (Un)	Group			
	Comparisons (n=44)	All patients (n=189)	S. enteritidis (n=140)	S. typhimurium (n=49)
<b>Intoxication index</b>				
<b>LII</b>	0.70±0.07	4.85±0.21 <i>a</i>	4.89±0.23 <i>a</i>	4.73±0.48 <i>a</i>
<b>ISL</b>	1.62±0.10	4.20±0.15 <i>a</i>	4.16±0.16 <i>a</i>	4.33±0.35 <i>a</i>
<b>HII</b>	0.64±0.06	6.03±0.32 <i>a</i>	6.09±0.33 <i>a</i>	5.87±0.76 <i>a</i>
<b>IIS</b>	0.16±0.02	5.22±0.37 <i>a</i>	5.41±0.43 <i>a</i>	4.68±0.77 <i>a</i>
<b>NRR</b>	12.75±1.82	69.91±3.58 <i>a</i>	70.53±3.70 <i>a</i>	68.14±8.94 <i>a</i>
<b>Indices of non-specific reactivity</b>				
<b>IR</b>	4.65±0.36	4.20±0.20	4.33±0.24	3.84±0.34
<b>NLR</b>	8.88±0.91	21.94±1.25 <i>a</i>	22.20±1.44 <i>a</i>	21.15±2.54 <i>a</i>
<b>LMR</b>	4.77±0.45	4.23±0.21	4.36±0.25	3.86±0.35
<b>I<sub>lymph</sub></b>	0.59±0.04	0.23±0.01 <i>a</i>	0.23±0.01 <i>a</i>	0.22±0.02 <i>a</i>
<b>ELR</b>	0.080±0.009	0.020±0.003 <i>a</i>	0.019±0.004 <i>a</i>	0.026±0.008 <i>a</i>
<b>IA</b>	1.05±0.07	0.37±0.01 <i>a</i>	0.38±0.01 <i>a</i>	0.37±0.02 <i>a</i>
<b>NI</b>	0.06±0.01	0.48±0.02 <i>a</i>	0.52±0.03 <i>a</i>	0.36±0.04 <i>a</i>
<b>Indices of inflammation activity</b>				
<b>KI</b>	2.02±0.94	5.64±0.24 <i>a</i>	5.52±0.25 <i>a</i>	5.95±0.56 <i>a</i>
<b>ILG</b>	4.85±0.29	2.09±0.07 <i>a</i>	2.11±0.08 <i>a</i>	2.02±0.13 <i>a</i>
<b>ILES<sub>R</sub></b>	1.33±0.20	2.32±0.13 <i>a</i>	2.39±0.16 <i>a</i>	2.11±0.23 <i>a</i>

Note. Significant difference of indicators ( $p < 0.05 - 0.001$ , Student's t-test was used): a – in respect of control group.

Increase in the following indexes was determined by hospitalization: LII – by 6.5 – 7.1, HII – by 8.5 – 10, ISL – by 2.5 – 2.7 ( $p < 0.05$ ) (table 1), that proves endogenous intoxication and inflammatory reaction in gastro-intestinal tract of patients from all groups. Reduction in number of eosinophils, lymphocytes and monocytes is observed and correspondingly growth of number of segmented forms of leukocytes [9, 10].

KI was increased by 2.7 – 2.9 ( $p < 0.05$ ), that indicates development of intoxication, inflammatory reaction of medium severity. ILES<sub>R</sub> increased by 1.7 – 1.8 ( $p < 0.05$ ), ILG reduced by 2.2 – 2.4 ( $p < 0.05$ ). NLR increased by 2.3 – 2.7 ( $p < 0.05$ ) (table 1). The indicators reflect differential leukocyte count shift to the left, activation of non-specific inflammatory process and probable development of autoimmune processes. Simultaneous increase in ISL and ILG reduction prove development of endogenous intoxication and disturbance of immunologic reactivity due to body autointoxication by destruction of own cells and by action of bacterial endo- and exotoxins [11 - 14], IR, LMR didn't change ( $p > 0.05$ ).

NRR was significantly increased in all examinations by 5.3 – 5.5 ( $p < 0.05$ ) (table 1), that proves decompensated endogenous intoxication [8].

$I_{lymph}$  reduced by 2.6 – 2.8 ( $p<0.05$ ) – it indicates active adaptive reaction of leukocytes and immunodeficient condition of cell type, in particular, reduction in non-specific anti-infective protection due to intoxication. ELR reduced by 3.3 – 4.4 ( $p<0.05$ ), IA – by 2.8 – 3 ( $p<0.05$ ) (table1). ELR reduction reflects predominance of delayed reactions over immediate hyperresponsiveness that leads to launching allergic mechanisms on the background of intoxication and finds its confirmation in IA changes [15].

NI was increased by 7 – 8.3 ( $p<0.05$ ) that reflects inflammatory reaction of medium severity, changes of white blood cell lineage to antigens or cytokine stimulation. Rise of index proves intoxication and disturbance of neutrophil ability of antigen elimination due to increase in number of young forms (stab neutrophils) [8]. Presence of acute inflammatory process reflects IIS that increases by 28.8 – 34 ( $p<0.05$ ) (table 1) [8].

Such changes of integrative hematological indexes happened both in men and in women and didn't depend on gender. There was a tendency for IIS, ILESR increase in women, NI increase – in men ( $t=1.76$ ;  $t=1.86$ ;  $t=1.89$  correspondingly, at  $t=1.97$   $p=0.05$ ) (table 2).

Table 2 – Integrative indicators of endogenous intoxication and immunoreactivity in patients with salmonellosis at hospitalization depending on gender identity (M±m)

Rate (Un)	Group			
	Comparisons (n=44)	All patients (n=189)	Men (n=121)	Women (n=68)
<b>Intoxication indices</b>				
<b>LII</b>	0.70±0.07	4.85±0.21 <i>a</i>	4.75±0.25 <i>a</i>	5.02±0.39 <i>a</i>
<b>ISL</b>	1.62±0.10	4.20±0.15 <i>a</i>	4.11±0.16 <i>a</i>	4.38±0.30 <i>a</i>
<b>HII</b>	0.64±0.06	6.03±0.32 <i>a</i>	5.76±0.37 <i>a</i>	6.51±0.59 <i>a</i>
<b>IIS</b>	0.16±0.02	5.22±0.37 <i>a</i>	4.68±0.40 <i>a</i>	6.18±0.75 <i>a</i>
<b>NRR</b>	12.75±1.82	69.91±3.58 <i>a</i>	71.63±4.77 <i>a</i>	66.87±5.24 <i>a</i>
<b>Indices of non-specific reactivity</b>				
<b>IR</b>	4.65±0.36	4.20±0.20	4.13±0.26	4.33±0.29
<b>NLR</b>	8.88±0.91	21.94±1.25 <i>a</i>	21.37±1.59 <i>a</i>	22.93±2.03 <i>a</i>
<b>LMR</b>	4.77±0.45	4.23±0.21	4.18±0.27	4.32±0.31
<b><math>I_{lymph}</math></b>	0.59±0.04	0.23±0.01 <i>a</i>	0.22±0.01 <i>a</i>	0.24±0.02 <i>a</i>
<b>ELR</b>	0.080±0.009	0.020±0.003 <i>a</i>	0.022±0.005 <i>a</i>	0.017±0.005 <i>a</i>
<b>IA</b>	1.05±0.07	0.37±0.01 <i>a</i>	0.37±0.01 <i>a</i>	0.39±0.02 <i>a</i>
<b>NI</b>	0.06±0.01	0.48±0.02 <i>a</i>	0.51±0.03 <i>a</i>	0.43±0.03 <i>a</i>
<b>Indices of inflammation activity</b>				
<b>KI</b>	2.02±0.94	5.64±0.24 <i>a</i>	5.52±0.25 <i>a</i>	5.84±0.49 <i>a</i>
<b>ILG</b>	4.85±0.29	2.09±0.07 <i>a</i>	2.03±0.07 <i>a</i>	2.19±0.14 <i>a</i>
<b>ILES</b>	1.33±0.20	2.32±0.13 <i>a</i>	2.12±0.14 <i>a</i>	2.67±0.26 <i>a</i>

Note. Significant difference of indicators ( $p<0.05$ – $0.001$ , Student's t-test was used): a – in respect of control group.

## Conclusions

1 *S. enteritidis* prevails in the etiological structure of disease, which more often caused diseases in women than in men. Peak of hospitalization by salmonellosis caused by *S. enteritidis* was in April – September, by *S. typhimurium* – June – September. Women sought medical aid more often in April – August, men – in June – September with maximum hospitalization in June and August.

Poultry eggs (prevailed in men), dairy products, meat – and fish products (prevailed in women), vegetables and fruit were among probable transmission factors. By salmonellosis caused by *S. typhimurium* more often than by *S. enteritidis*, transmission factors were eggs, meat, fish products, sausages; by *S. enteritidis* – dairy products, vegetables and fruit.

2 Predominantly men of young age are affected. Gastroenteritic variant prevails in all patients irrespective of gender, the second by frequency is gastroenterocolitic (more rarely in women,  $p < 0.05$ ), the third is enterocolitic variant, enteric one was met more rarely (prevailing in women  $p < 0.01$ ). Dependence on distribution of clinical variants from etiology was not found.

3 By patient hospitalization basic complaints were of weakness, temperature raise, diarrhea, nausea, vomiting, pain in different abdominal areas (more often in mesogastrium and epigastrium), additions of mucus in feces. Predominance of the following complaints has been established by gender: in women – of nausea, pain in epigastrium and in the left iliac region, headache, additions of mucus in feces, in men – pain in hypogastrium.

4 Basic objective signs of salmonellosis were dehydration and abdominal pain by palpation (more often in mesogastrium and epigastrium, more rarely – in the right iliac region, rarely – in hypogastrium and the left iliac region), increased bowel sounds by palpation, increase in liver sizes. Temperature increase was more intensively at pre-hospital stage than at hospitalization. Symptom dependence on gender and etiology was determined – increase in liver sizes, pain in hypogastrium and spasm of sigmoid colon were more often detected. Pain syndrome in mesogastrium and hypogastrium were more often determined by salmonellosis caused by *S. typhimurium*.

5 By hospitalization changes of integrative indexes of endogenous intoxication were detected: increase in LII, ISL, HII, IIS, NRR, NLR, ILESR, NI; reduction in ILG,  $I_{lymph}$ , ELR, IA. There were no authentic changes of IR and LMR, although there was a tendency to its reduction by salmonellosis caused by *S. typhimurium*. Such changes of integrative hematological indices occurred both in men and women and didn't depend on age. There was a tendency for increase in IIS, ILESR (in women) and NI (in men).

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