VER
Vascular & Endovascular Review

Phase Characteristics of Changes in Autonomic Homeostasis in Children with Acute Intestinal Infections: A Case Study of Salmonellosis

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ABSTRACT

To date, numerous mechanisms of the pathogenesis of intestinal infections in children have been clarified based on the results of various studies. However, the role of reflex and humoral factors of the autonomic division of the central nervous system in the development of vegetative–visceral dysfunctions remains insufficiently understood. According to the theory of H. Selye and A.A. Koltypin, these dysfunctions have a phasic character and, regardless of etiology, are determined by the continuity in the functional activity of the leading mechanisms of autonomic support—sympathoadrenal, parasympathetic, and humoral. Comprehensive information on the state of autonomic homeostasis in a sick child can be obtained only by correlating clinical observations with biochemical and functional diagnostic methods. We found no publications containing such complex investigations in children with intestinal infections, particularly in patients with salmonellosis.

KEYWORDS: Pathogenesis, Phasic Characteristics, Autonomic Homeostasis, Young Children, Severe Intestinal Infections, Cellular Membranes.

How to Cite: Shadie Kurtieva, Feruza Ibragimova, Nigora Alikulova, Saodat Yarmukhamedova, Lola Yuldasheva, (2025) Phase Characteristics of Changes in Autonomic Homeostasis in Children with Acute Intestinal Infections: A Case Study of Salmonellosis, Vol.8, No.18s, 408-413.

STUDY OBJECTIVE

The aim of this work was to investigate clinical, biochemical, and instrumental indicators of autonomic homeostasis in **146 young children** with salmonellosis. In this report, we present the results of the **second part** of the study, including clinical findings, instrumental parameters, and features of structural–functional alterations of cellular membranes, using leukocytes as a model—since the structural–functional organization of cell membranes is considered the final component of adaptive processes.

MATERIALS AND METHODS

Clinical–anamnestic data, standard laboratory tests (complete blood count, coagulation profile, electrolytes, blood glucose), and instrumental examinations were used: cardiointervalography, electrocardiography, EEG. Leukocyte cell membrane components were evaluated, including:

- LPC — lysophosphatidylcholine
- PS — phosphatidylserine
- SM — sphingomyelin
- PC — phosphatidylcholine
- PEA — phosphatidylethanolamine
- EOF — easily oxidizable phospholipids (PS + PEA)
- TOF — resistant phospholipids (PC + SM)

Interaction of cell membranes with specific membrane-active mediators of the autonomic nervous system and steroid hormones was also assessed.

RESULTS AND DISCUSSION

According to the theory of H. Selye and A.A. Koltypin, autonomic dysfunctions during acute pathological processes have a **phasic nature**, with an inevitable sequence in the activity of the main autonomic regulatory mechanisms. Based on this, it was essential to study the clinical manifestations of acute intestinal diseases—specifically severe forms of salmonellosis in young children—in correlation with the state of the leading mechanisms of adaptive regulation: sympathoadrenal, parasympathetic, and neurohumoral.

Further identical investigations were performed in other acute gastrointestinal disorders and intestinal infections. Their results confirmed the findings of this study, indicating the **universal character** of the revealed patterns. Detailed data will be presented in subsequent publications.

The conducted research confirmed the validity of the working hypothesis.

A detailed analysis of the clinical–functional manifestations of salmonellosis in young children revealed distinct **phases of autonomic nervous system responses** to the toxin, corresponding to clinical symptoms of the disease. This analysis was guided by our previously developed original table of diagnostic criteria for clinical and pathophysiological manifestations of autonomic regulation in severe salmonellosis in early childhood.

Most children with both gastrointestinal and generalized forms were admitted with symptoms characteristic of the **sympathoadrenal phase**, manifested by: high fever, pale skin, dry mucous membranes, restlessness or agitation, frequent convulsions, tachycardia, elevated blood pressure, moderate dyspnea, and increased blood coagulation potential (hypercoagulability). Subsequently, the sympathoadrenal phase shifted to the **parasympathetic phase**, which varied in severity and prognosis.

With adequate therapy and clinical improvement, the parasympathetic phase reflected a reorganizing autonomic homeostasis, supporting restoration of normal physiological functions.

However, in unfavorable cases, the parasympathetic phase represented a **pre-terminal stage**, and unlike the favorable course that resolved in recovery, it was accompanied by symptoms of pre-terminal dysfunctions in affected children. The unfavorable parasympathetic variant, in addition to a high risk of mortality, also indicated a high probability of prolonged or complicated salmonellosis.

Despite some overlap in symptoms of favorable and unfavorable parasympathetic phases, distinct differences with significant prognostic value were identified.

The transition into the parasympathetic phase with a **favorable prognosis** was characterized by a reduction in symptoms of general intoxication, a decrease in body temperature to subfebrile levels, and a shift from restlessness or agitation to lethargy. Convulsive episodes resolved, moderate signs of microcirculatory disturbances appeared (mottled skin pattern, cyanosis of the nails and lips, positive Gvedal symptom), and both systolic and diastolic blood pressure decreased proportionally. Oliguria, frequent appearance of blood in the stool, and a shift from a hypercoagulable to a hypocoagulable state were also observed.

The transition into the parasympathetic phase with an **unfavorable course** was marked by a fall in body temperature with a tendency toward hypothermia, a predominant decrease in systolic and pulse pressure, bradyarrhythmia or, conversely, rhythm rigidity, dyspnea, anuria, hypocoagulation, pathological fibrinogenemia, presence of blood in the stool, coffee-ground vomiting, and occasionally intestinal bleeding. These signs correspond to clinical manifestations of **infectious–toxic shock grade II–III**, representing a state of decompensation and exhaustion of adaptive mechanisms.

The clinical observations were confirmed by cardiointervalographic (CIG) data based on heart rate variability. According to CIG performed in the supine position, children admitted to the clinic predominantly exhibited a **sympathicotonic baseline autonomic tone (BAT)**.

Table 1. Cardiointervalography (CIG) Parameters in Children With Salmonellosis Depending on the Form and Phase of the Disease

Timing & Position	Mo, s	Amo %	Δx, s	IN (units)	IN2/IN1
1st day – Supine	0.40 ± 0.05*	46.62 ± 2.56***	0.10 ± 0.02*	591.1 ± 38.16***	1.71 ± 0.08***
1st day – Supine	0.30 ± 0.05**	54.50 ± 2.46***	0.12 ± 0.02*	708.7 ± 41.27***	1.32 ± 0.09
1st day – Orthostasis	0.33 ± 0.02**	60.08 ± 3.11***	0.09 ± 0.03*	1013.7 ± 59.21***	
1st day – Orthostasis	0.32 ± 0.04*	50.61 ± 2.73***	0.09 ± 0.01**	935.2 ± 52.61***	
7th day – Supine	0.75 ± 0.05**	23.62 ± 1.14*	0.40 ± 0.05*	40.8 ± 5.81***	1.45 ± 0.06

7th day – Supine	0.98 ± 0.14*	35.76 ± 1.71*	0.29 ± 0.07	63.1 ± 7.04***	0.86 ± 0.04***
7th day – Orthostasis	0.37 ± 0.04*	21.34 ± 1.56***	0.37 ± 0.03*	77.9 ± 6.24***	
7th day – Orthostasis	0.81 ± 0.07**	23.04 ± 1.04***	0.26 ± 0.06	54.3 ± 6.22	
Healthy Children (Supine/Ortho)	0.61 ± 0.08 / 0.57 ± 0.09	20.09 ± 2.39 / 32.3 ± 2.53	0.24 ± 0.06 / 0.21 ± 0.05	130.9 ± 24.17 / 184.4 ± 25.12	1.41 ± 0.03

Note: The numerator contains data from patients with the gastrointestinal form, and the denominator contains data from patients with the generalized form. Asterisks indicate statistically significant differences compared with healthy children: one asterisk – $p < 0.05$; two asterisks – $p < 0.01$; three asterisks – $p < 0.001$.

Initial sympathicotonia was detected more frequently in the gastrointestinal form of salmonellosis (71.43%) than in the generalized form (48.18%). Conversely, vagotonic initial autonomic tone (IAT) was more common in the generalized form (31.71%) than in the gastrointestinal form (10.47%).

The predominance of initial sympathicotonia in patients with both clinical forms of salmonellosis—more markedly in the gastrointestinal form—indicated activation of sympathoadrenal compensatory mechanisms. At the same time, the relatively higher frequency of initial vagotonia (compared with the gastrointestinal form) in patients with the generalized form suggested exhaustion of compensatory–adaptive mechanisms of the autonomic nervous system (ANS). The presence of eutonía in a small number of patients did not signify the absence of an autonomic response to salmonellosis. Analysis of their clinical symptoms revealed simultaneous activity of both sympathetic and parasympathetic divisions. These were primarily patients admitted during the transitional phase of the illness, clinically characterized by emerging activation of the parasympathetic division against a background of persisting, though diminishing, sympathoadrenal responses. This fact underscores the necessity of prioritizing clinical signs when assessing autonomic status, and using cardiointervalography indicators only as supporting data.

Cardiointervalography performed on the 7th day of hospitalization demonstrated a marked predominance of parasympathetic autonomic reactions in both groups, which corresponded with clinical observations.

Among patients with the gastrointestinal form of salmonellosis, 83.81% were children with vagotonic IAT, while among those with the generalized form this proportion was 85.37%. The remaining children exhibited eutonia. Virtually no patients displayed sympathicotonic IAT. Thus, the majority of hospitalized patients were in the parasympathetic phase of the disease by day 7.
Cardiointervalographic studies conducted on days 1 and 7 of hospitalization in the orthostatic position—with calculation of the IN2/IN1 coefficient and assessment of autonomic reactivity—showed that upon admission, asympathicotonic autonomic reactivity predominated in both forms of the disease (36.19% and 46.34% respectively).

By day 7, the frequency of asympathicotonic AR increased to 74.29% and 85.37% respectively; notably, no children with the generalized form exhibited hypersympathicotonic AR, and among those with the gastrointestinal form, such cases accounted for only 2.86%. Thus, the parasympathetic phase was characterized by depletion of compensatory sympathoadrenal mechanisms. The depth of this depletion may be reflected by the IN2/IN1 coefficient. Our observations indicate that a decrease of this coefficient below 0.66, in the presence of initial vagotonia and sympathicotonic AR, predicts a prolonged course of salmonellosis and a high risk of fatal outcome.

Further analysis of the phase-specific nature of clinical manifestations demonstrated their clear association with chronobiological patterns. Specifically, the critical period typically occurred within the first three days. Subsequently, within the framework of a near-weekly rhythm, a transitional phase emerged, and finally—within a near-nine-day rhythm—processes of stabilization and resolution of infectious toxicosis became most pronounced. Overall, the sympathoadrenal phase corresponds to the first three days of illness; the next three days represent a transitional period; and the third near-three-day cycle marks the onset of the parasympathetic phase, provided the disease follows an acute course. Among examined patients with the gastrointestinal form, the average duration of the sympathoadrenal phase was 3.33 ± 0.30 days, whereas in the generalized form it was 2.09 ± 0.04 days; the duration of the parasympathetic phase was 13.05 ± 0.85 and 17.90 ± 1.5 days, respectively.

Thus, summarizing these clinical observations, one may conclude that the infectious process exhibits a phased course, with a consistent transition from a sympathoadrenal phase to a parasympathetic phase, and recovery is characterized by a state of eutonia. This pattern aligns with the concepts developed by A.A. Koltypin and H. Selye concerning the phase-specific stereotypy of autonomic nervous system responses to infectious agents and other stressors.

While the sympathoadrenal phase proceeds in a relatively uniform manner—differing mainly in quantitative intensity—the parasympathetic phase is more complex: on the one hand, it represents increased activity of autonomic mechanisms aimed at supporting anabolic and reparative processes; on the other hand, parasympathetic predominance may, in some cases, lead to adaptive failure and the development of life-threatening conditions in affected children. This consideration, which expands the understanding of the phase structure of stress—including salmonellosis—must undoubtedly be taken into account in intensive care.

The lability of individual phases of infectious–toxic stress depends on multiple factors, including constitutional and genetic characteristics of the child, the virulence of the pathogen, and the adaptive capacity of the body's functional systems.

At the same time, the phase structure of infectious stress reflects the organism's adaptive responses, which constitute a hierarchical system involving higher autonomic mechanisms, intermediate mechanisms at the level of hemodynamics and blood rheology, and effector mechanisms at the membrane–cell level and within extra- and intracellular metabolic systems. To date, alterations in hemodynamics and in blood rheology in pediatric salmonellosis have been studied extensively, which is also reflected in our traditional investigations.

Subsequent analysis of the functional activity and reserve capacity of adaptive reactions during the course of salmonellosis in children—based on an assessment of structural and functional alterations of cellular membranes—confirmed their significance in the processes of pathogenesis and recovery. Furthermore, given scientific evidence that membrane-destructive processes underlie all infectious diseases, and that their depth and extent ultimately determine disease severity and outcome, we conducted a series of studies characterizing the state of cellular membranes.

These investigations were particularly relevant because the structural–functional organization of cellular membranes is considered the final link in adaptive processes. At the same time, it should be noted that the relationship between clinical manifestations of acute intestinal infections, including salmonellosis in young children, autonomic dysfunction (sympathoadrenal and parasympathetic), and structural–functional abnormalities of cellular membranes has not been previously addressed.

Table 2. Content and Ratio of Major Phospholipid Fractions in Leukocytes of Young Children with the Gastrointestinal Form of Salmonellosis during the Course of the Disease (nmol per 10^9 cells)

Indicators	Acute Phase	Recovery	Healthy Children
LFX	10.90 ± 1.10***	8.96 ± 1.21*	5.81 ± 0.58
FS	2.69 ± 0.52*	3.67 ± 0.41	4.79 ± 0.66
SM	5.59 ± 0.77	5.32 ± 0.42	6.13 ± 0.89
FX	7.26 ± 0.80*	8.75 ± 0.81	9.38 ± 0.66
FEA	2.08 ± 0.11***	2.29 ± 0.14*	2.68 ± 0.10
LOF/TOF	0.41	0.46	0.48
LFX/FX	1.48	1.02	0.62

Note: Abbreviations:
LPC – lysophosphatidylcholine;
PS – phosphatidylserine;
SM – sphingomyelin;
PC – phosphatidylcholine;
PEA – phosphatidylethanolamine;
EOP – easily oxidized phospholipids (PS + PEA);
ROP – resistant-to-oxidation phospholipids [PC + SM].
Asterisks indicate statistically significant differences compared with healthy children:
one asterisk – $p < 0.05$, two asterisks – $p < 0.01$, three asterisks – $p < 0.001$.

Thus, an analysis of the content and proportional distribution of the major structural–metabolic components of cellular membranes—namely phospholipids (using leukocytes as a model)—revealed a distinct pattern of alterations that may be characterized in terms of adaptive and maladaptive manifestations of salmonellosis. Maladaptive changes were reflected in:

1. **A decrease in the content of easily oxidized, metabolically active phospholipid fractions in leukocytes.** These fractions are the first to be recruited into peroxidation processes and mobilized to replenish the organism's energy reserves. Their depletion naturally reduces the metabolic functions of cellular membranes, since most membrane-bound enzymes responsible for sustaining cellular activity are phospholipid-dependent.
2. **Pathological lysis of membrane phospholipids** resulting from excessive activity of endogenous phospholipases. This was evidenced by the accumulation of degraded phospholipid forms—lysophospholipids—identified through increased lysophosphatidylcholine levels. Lysophosphatidylcholine, in turn, may exert a secondary membrane-detergent effect and diminishes the functional–metabolic activity of the cellular membrane by disrupting transmembrane transport and energy exchange processes.

Adaptive responses in the structural–functional organization of cellular membranes during the phase of clinically manifested salmonellosis included **the phenomenon of metabolic inertness of resistant-to-oxidation phospholipids**. Changes in phosphatidylcholine content were moderate, and sphingomyelin levels did not change significantly ($p < 0.05$). All these shifts influenced the balance between easily oxidized and resistant phospholipid fractions, shifting it toward the predominance of resistant phospholipid structures.

Table 3. Content and Ratio of Major Phospholipid Fractions in Leukocytes of Young Children with the Generalized Form of Salmonellosis in the Course of the Disease (nmol per 10^9 cells)

Table: Phospholipid Fractions in Leukocytes

Indicators	Acute Phase	Recovery	Healthy Children
ЛФХ	20.36 ± 2.01***	12.59 ± 1.69***	5.81 ± 0.58

ФС	2.19 ± 0.64**	2.30 ± 0.71*	4.79 ± 0.66
СМ	6.91 ± 0.56	6.58 ± 0.44	6.13 ± 0.89
ФХ	6.04 ± 0.61***	7.26 ± 0.77*	9.38 ± 0.66
ФЭА	1.03 ± 0.19***	1.58 ± 0.23***	2.68 ± 0.10
ЛОФ/ТОФ	0.25	0.46	0.48
ЛФХ/ФХ	3.31	1.02	0.62

Note: Abbreviations: LPC – lysophosphatidylcholine; PS – phosphatidylserine; SM – sphingomyelin; PC – phosphatidylcholine; PEA – phosphatidylethanolamine; EOP – easily oxidized phospholipids (PS + PEA); ROP – resistant-to-oxidation phospholipids [PC + SM].
An asterisk indicates statistically significant differences compared with the data of healthy children: one asterisk – $p < 0.05$, two asterisks – $p < 0.01$, three asterisks – $p < 0.001$.

The pathogenetic significance of the identified alterations in the structural organization of cellular membranes is supported by a clear correlation between quantitative indicators and the severity of the disease; specifically, these alterations were more pronounced in the generalized form. At the same time, analysis of the dynamics of these changes throughout the course of the illness indicates a substantial role of cellular membrane repair in shaping the mechanisms of sanogenesis and ensuring a favorable clinical outcome. Restoration of membrane structure correlated with the resolution of clinical manifestations.

Structural disorganization of cellular membranes at the level of their phospholipid composition in pediatric salmonellosis also affected other functional physicochemical constants of the membranes. This was confirmed by findings from studies assessing the interaction of cellular membranes with specific membrane-tropic mediators of the autonomic nervous system and with steroid hormones. More detailed results of these investigations will be presented in forthcoming publications.

During the examination of erythrocyte membrane interactions with prednisolone in the presence of the HTC probe, it was established that during the acute phase of both forms of salmonellosis (more markedly in the generalized form), glucocorticoid (prednisolone) uptake increased and subsequently decreased during recovery. This phenomenon appears to be regular, given that glucocorticoid hormones serve as mediators of sympathoadrenal influences within the autonomic nervous system.

Based on these findings, the use of glucocorticoids may be considered necessary in the acute stage of salmonellosis.
In addition, a clear continuity in membrane sensitivity to adrenaline and acetylcholine was identified. During the manifestation stage of clinical symptoms (the sympathoadrenal phase), cellular membrane receptors were most responsive to adrenaline. In the phase of clinical improvement—the parasympathetic phase of infectious stress—membrane receptor sensitivity to acetylcholine, the mediator of parasympathetic mechanisms of the autonomic nervous system, increased. These findings confirm the previously proposed concept of the phase-vegetative structure of infectious stress in children with salmonellosis.

The phasic nature of salmonellosis progression in children was further supported by correlations between indicators of functional activity of key autonomic nervous system mechanisms and indicators of interaction between specific mediators and cellular membranes over time.

In summary, the results allow us to conclude that, in its pathophysiological essence, salmonellosis in children represents a variant of membrane pathology accompanied by pronounced autonomic dysfunction. This conclusion outlines promising directions for further development of interventions aimed at correcting pathophysiological changes in children with salmonellosis.

CONCLUSIONS

1. Salmonellosis in young children is characterized by a phasic course with a consistent succession of autonomic clinical and pathophysiological manifestations, involving a sequential transition from the sympathoadrenal phase to the parasympathetic phase.
2. Clinically, the sympathoadrenal phase presents with characteristic intoxication: high fever; neurological disturbances (restlessness, agitation, seizures); microcirculatory disorders (pale skin, moderate cyanosis of the lips and nails, cold extremities); impaired central circulation (tachycardia, elevated or normal blood pressure); dyspnea; reduced urine output; and blood coagulation abnormalities—hypercoagulation.
   The parasympathetic phase is distinguished by decreased body temperature, a shift from restlessness to lethargy, pronounced microcirculatory disorders (mottled pale-gray skin, cyanosis of lips and nails, cold extremities), bradycardia or tachycardia, muffled heart tones, decreased blood pressure, dyspnea, reduced urine output, and a transition from hypercoagulation to hypocoagulation.
3. In severe forms of salmonellosis, the parasympathetic phase may follow either a favorable course (leading to recovery) or an unfavorable course. In the latter, characteristic parasympathetic symptoms progressively worsen, reflecting exhaustion of adaptive mechanisms and manifesting clinically as infectious–toxic shock.
4. The phasic pattern and severity of autonomic clinical-pathophysiological manifestations correlate with cardiointervalography data, which may serve as additional criteria for assessing disease severity.
5. The peak period of clinical manifestations in children is characterized by structural and functional changes in cellular membranes, which include both adaptive features (accumulation of resistant phospholipid fractions in the lipid bilayer) and maladaptive features (accumulation of lysophospholipid forms).

6. Structural-functional reorganization of cell membranes in salmonellosis also manifests as altered sensitivity of membrane receptors to mediators of the sympathoadrenal and parasympathetic divisions of the autonomic nervous system—adrenaline and acetylcholine—as well as to prednisolone, which reflects sympathoadrenal stimulation. These changes closely correlate with the autonomic phases of the pathology: increased sensitivity to adrenaline and prednisolone is observed in the sympathoadrenal phase, whereas increased sensitivity to acetylcholine is observed in the parasympathetic phase.

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