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Maternal Dysbiosis Alters Systemic Osmoregulation and Organ Wet Weights Following Hemorrhagic Shock in Rats

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ABSTRACT

Hemorrhagic shock is a major cause of trauma-related mortality, yet the contribution of the gut microbiome to systemic fluid and electrolyte regulation during acute blood loss remains unclear. This study investigated whether maternal antibiotic-induced dysbiosis alters the osmoregulatory and metabolic responses of offspring to hemorrhagic shock. Pregnant and lactating Sprague Dawley dams received vancomycin and amoxicillin, and antibiotic treatment was continued in male offspring until 8 weeks of age. Following a 4-week washout period, 12-week-old offspring underwent fixed-volume hemorrhagic shock (1.5 mL/100 g body weight), and serum biochemical variables and organ wet weights were evaluated. Compared with controls, dysbiotic offspring exhibited persistent hypernatremia and hyperchloremia (both $p < 0.001$), together with significantly higher calculated serum osmolarity ($p = 0.030$). These alterations were accompanied by significantly lower blood urea nitrogen and creatinine concentrations ($p < 0.01$), suggesting an attenuated metabolic and renal adaptive response. Lung and brain wet weights were also significantly lower in dysbiotic offspring ($p = 0.002$ and $p = 0.01$, respectively), whereas kidney and heart wet weights were unaffected. These findings suggest that maternal antibiotic-induced dysbiosis is associated with impaired systemic electrolyte regulation and organ-specific physiological responses during hemorrhagic stress. Clinically, closer monitoring of serum sodium and osmolarity may be warranted in trauma patients with a history of prolonged antibiotic exposure.

Keywords: *Gut-lung axis, Hemorrhagic shock, Maternal dysbiosis, Osmoregulation, Pulmonary desiccation.*

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1. Introduction

The maintenance of body fluid and electrolyte balance is a fundamental prerequisite for survival, with sodium homeostasis serving as a central point of physiological stability. Sodium regulation is not merely a renal task but a complex systemic orchestration involving neurohormonal, vascular, and intestinal components [1]. While the gastrointestinal tract is traditionally recognized for nutrient absorption, its mucosa functions as a critical interface for water reclamation and electrolyte exchange. Recent advances in pathophysiology have expanded this understanding, defining the gut-lung axis as a bidirectional communication pathway where intestinal perturbations fundamentally shape pulmonary health [2]. Intestinal dysbiosis in developing rodents is sufficient to drive distal pulmonary vascular remodeling and hypertension, confirming that gut-derived signals actively determine lung structure [3]. Similarly, gut microbiota dysbiosis may compromise pulmonary immune responses and tissue integrity [4]. These findings support the concept that intestinal barrier integrity and microbial composition contribute to respiratory resilience. However, existing literature has predominantly focused on immune-mediated pathways. The role of the microbiome in regulating systemic fluid dynamics and electrolyte homeostasis, particularly during hemodynamic stress, remains a knowledge gap.

Under physiological conditions, the colonic mucosa serves as a primary site for water and electrolyte reclamation, a process heavily dependent on microbial metabolites [5]. When this microbial ecosystem is disrupted, a state known as dysbiosis, systemic fluid and electrolyte homeostasis may also be affected [6]. One potential consequence of dysbiosis is impairment of the intestinal barrier. Dysbiotic insults have been reported to downregulate tight-junction proteins such as occludin and zonula occludens-1, thereby increasing intestinal permeability [7]. This barrier dysfunction may facilitate the translocation of living bacteria and endotoxins into the systemic circulation, contributing to systemic inflammation [8]. Consequently, the kidney, which is highly vascularized and sensitive to circulating factors, may become vulnerable to gut-derived inflammatory and

metabolic signals. Evidence linking increased intestinal permeability with renal inflammation and immune-cell infiltration supports the existence of a functionally relevant gut–kidney axis [9].

The progression from gut barrier failure to renal dysfunction may involve changes in microbial metabolites, uremic toxins, and inflammatory signaling. Gut dysbiosis has been associated with the accumulation of uremic toxins and the induction of chronic systemic inflammation, which may impair renal adaptability [10]. Dysbiosis increases the systemic load of specific toxins such as indoxyl sulfate, which induces renal oxidative stress and functional decline [11]. Supporting this, Yu et al. [12] reported that gut dysbiosis significantly contributes to the circulating pool of uremic toxins, thereby accelerating renal dysfunction and metabolic instability even in the absence of primary kidney disease. At the cellular level, these gut-derived toxins trigger renal tubular injury and interstitial fibrosis via the activation of the NLRP3 inflammasome [13]. Collectively, these findings suggest that dysbiosis could reduce renal adaptive capacity before an acute hemodynamic insult, although this possibility was not directly evaluated in the present study.

The functional consequences of these alterations may include disruption of the neurohormonal systems responsible for fluid and sodium regulation. Gut dysbiosis has been associated with activation of the systemic renin–angiotensin–aldosterone system and the sympathetic nervous system [14]. Microbiota-derived short-chain fatty acids, including acetate and propionate, may also influence blood pressure and renin secretion through G-protein-coupled receptors such as GPR41/FFAR3 and Olfr78 [24]. Altered production of these metabolites may therefore provide a potential link between gut microbial disturbance and impaired renal compensation. This systemic neurohormonal shift may promote sodium retention and volume expansion as a maladaptive response to inflammation. Lu et al. [15] further localized this effect, reporting that dysbiosis induces aberrant activation of the intrarenal renin–angiotensin system specifically within kidney tissue. As the renin–angiotensin system is a major regulator of sodium retention, its overactivation combined with tubular injury may create a predisposition to systemic electrolyte disturbances [16].

This vulnerability may become particularly relevant when the host is subjected to a second hit, such as hemorrhagic shock. Hemorrhagic shock necessitates a rapid shift of fluids from the intracellular and interstitial compartments into the vasculature to preserve cardiac preload, a process known as autotransfusion [17]. In a healthy host, this is a fundamental survival mechanism. However, in a host with altered renal electrolyte handling, this compensatory response may contribute to disturbances in systemic tonicity. The stress of shock itself may further exacerbate the underlying gut pathology. Acute systemic insults can rapidly induce additional microbial and barrier disturbances, creating a potential cycle of intestinal dysfunction and systemic inflammation [18]. Similarly, Li et al. [19] demonstrated that sepsis, a systemic stressor analogous to shock, significantly worsens intestinal microbiota composition and inflammation, suggesting that the gut-kidney and gut-lung axes may be particularly vulnerable to physiological stress. Elevated extracellular sodium may promote osmotic movement of water from intracellular to extracellular compartments; however, serum electrolyte concentrations alone cannot establish tissue dehydration [1]. The lungs were selected as a principal organ of interest because of the established gut-lung axis and their sensitivity to rapid vascular and fluid shifts during hemorrhagic stress [20].

Therefore, this study aimed to investigate the impact of maternal antibiotic-induced dysbiosis, with continued antibiotic exposure in offspring until 8 weeks of age, on systemic biochemical responses and organ wet weights following hemorrhagic shock. Specifically, we examined whether dysbiotic offspring exhibited altered serum sodium, potassium, chloride, blood urea nitrogen, creatinine, and calculated serum osmolarity, together with differences in the absolute wet weights of the lungs, brain, kidneys, and heart. We hypothesized that offspring subjected to the antibiotic-induced dysbiosis protocol would display altered electrolyte and calculated osmolarity profiles and organ-specific differences in post-hemorrhage wet weights compared with control offspring.

2. Materials and Methods

2.1 Ethical Statement and Animals

A total of nine pathogen-free, synchronously pregnant Sprague Dawley dams (aged 2-3 months) were supplied by the Experimental Animal Breeding Center of Bursa Uludağ University. The detection of a vaginal plug designated the first day of gestation. Dams were individually housed in polycarbonate cages within a specific pathogen-free facility, featuring a standard 12-hour light/dark cycle and an ambient temperature of 20-24°C. Standard rodent diet and tap water were available ad libitum. All animal handling and experimental protocols received ethical clearance from the Bursa Uludağ University Animal Experimentation Local Ethics Committee (Approval: 2024-03/03).

2.2 Establishment of Maternal Dysbiosis and Vertical Transmission Model

An early-life dysbiosis model combining maternal and direct offspring antibiotic exposure was used to perturb microbial colonization during development. Following synchronized mating of nine female Sprague Dawley rats, pregnancy status was evaluated during mid-gestation. Six dams with confirmed viable pregnancies were retained and equally assigned to the Control and Dysbiosis groups, with three dams in each group. The other three females were excluded before initiation of the experimental treatment. To limit potential bias arising from a single maternal source, the seven male offspring included in each adult experimental group were selected by random draw from the three corresponding litters. Each dam contributed no more than two to three male pups to the final cohort. Beginning 10 days before parturition, dams assigned to the Dysbiosis group received amoxicillin and vancomycin in their drinking water. Fresh antibiotic-containing water was prepared daily to provide amoxicillin at 60 mg/kg body weight and vancomycin at 8 mg/kg body

weight, corresponding to final concentrations of 0.6 mg/mL and 0.08 mg/mL, respectively. These concentrations were calculated based on an estimated daily water intake of 10–12 mL/100 g body weight. Antibiotic administration continued throughout the lactation period. After weaning at 4 weeks of age, male offspring in the Dysbiosis group remained on the same antibiotic regimen until 8 weeks of age. Antibiotics were subsequently withdrawn for 4 weeks, covering weeks 9–12, before induction of hemorrhagic shock. This antibiotic-free interval was included to reduce the influence of ongoing or acute drug exposure and to allow evaluation of sustained physiological effects associated with early-life microbiome disruption. Animals in the Control group received untreated drinking water throughout the entire experimental period.

2.3 Surgical Procedure and Hemorrhagic Shock Protocol

A volume-controlled hemorrhagic shock protocol was executed on 12-week-old rats following. The subjects were anesthetized using an intramuscular combination of ketamine (70 mg/kg) and xylazine (10 mg/kg), with their body temperature continuously regulated at 37°C via a heating pad. Hemorrhage was induced through the cannulation of the left femoral artery, whereby a standardized blood volume (1.5 mL per 100 g body weight) was extracted over a duration of 10 minutes.

2.4 Biochemical Analysis and Organ Gravimetry

Following the hemorrhagic shock protocol (60 mins post-shock), blood samples were collected to assess systemic fluid-electrolyte balance and hydration status. Serum was separated by centrifugation at 3000 rpm for 10 minutes. To evaluate the dehydration hypothesis, serum concentrations of Sodium (Na+), Potassium (K+), and Chloride (Cl-) were analyzed using automatic analyzer (Roche Cobas C702 Chemistry Analyzer, Germany). Calculated serum osmolarity was estimated using the following equation: calculated serum osmolarity (mOsm/L) = 2 × serum sodium (mmol/L) + serum glucose (mg/dL)/18 + BUN (mg/dL)/2.8. Because serum osmolality was not measured directly using an osmometer, the calculated values were considered indirect estimates of serum osmolarity [36]. Immediately following blood collection and euthanasia, a gross necropsy was performed. Vital organs, specifically the lungs, brain, heart, and kidneys, were carefully harvested, washed in cold saline to remove excess blood, blotted dry, and weighed using a precision electronic balance. Organ weights were recorded to evaluate dehydration-associated structural atrophy and specific end-organ mass loss.

2.5 Statistical Analysis

Quantitative results are presented as the Mean ± Standard Error of the Mean (SEM) with a sample size of n=7 per group. To analyze biochemical fluctuations over time (pre- and post-hemorrhage) alongside group interactions, a Two-way Repeated Measures Analysis of Variance (ANOVA) was conducted, with Bonferroni adjustments applied for multiple comparisons. For variables measured at a single time point, such as organ weights, an unpaired Student's t-test was utilized to assess differences between the Control and Dysbiosis cohorts. Statistical significance was established at a threshold of $p < 0.05$.

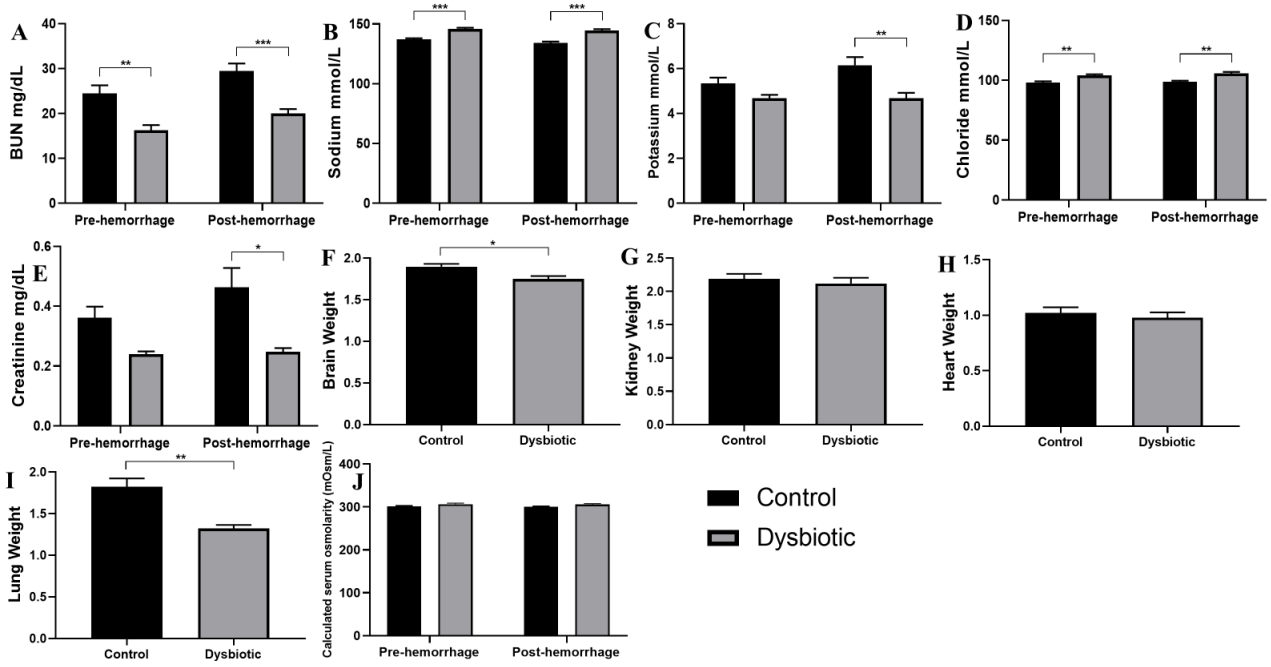

Figure 1. Impact of maternal dysbiosis on serum electrolyte homeostasis and vital organ gravimetry following hemorrhagic shock. Serum levels of (A) Blood Urea Nitrogen (BUN), (E) Creatinine, (B) Sodium (Na^+), (C) Potassium (K^+), and (D) Chloride (Cl^-). Wet organ weights of the (F) brain, (G) kidney, (H) heart, (I) lung, and (J) Calculated serum osmolarity before and after hemorrhage. Black bars represent the Control group; gray bars represent the Dysbiosis group. Data are presented as mean ± SEM (n=7/group). Statistical significance compared to the Control group: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

3. Results

3.1 Maternal Dysbiosis Is Associated with a Distinct Pre-Hemorrhage Osmoregulatory Profile

Prior to hemorrhage, significant differences were observed in several serum biochemical variables between the experimental groups. Blood urea nitrogen (BUN) concentration was significantly lower in the Dysbiosis group than in the Control group (16.26 ± 1.160 vs. 24.44 ± 1.846 mg/dL, respectively; $p = 0.002$) (Figure 1A). In contrast, serum sodium concentration was significantly higher in the Dysbiosis group than in the Control group (145.8 ± 0.970 vs. 137.2 ± 0.917 mmol/L, respectively; $p < 0.001$) (Figure 1B). Serum chloride concentration was also significantly higher in the Dysbiosis group than in the Control group (104.0 ± 1.095 vs. 98.2 ± 0.970 mmol/L, respectively; $p = 0.004$) (Figure 1D). Collectively, these findings indicate that maternal dysbiosis was associated with a distinct pre-hemorrhage biochemical profile characterized by altered serum electrolyte and BUN concentrations.

3.2 Maternal Dysbiosis Is Associated with an Altered Biochemical Response to Hemorrhage

Following hemorrhage, serum sodium concentration remained significantly higher in the Dysbiosis group than in the Control group (144.6 ± 1.030 vs. 134.2 ± 1.114 mmol/L, respectively; $p < 0.001$) (Figure 1B). Serum potassium concentration was significantly lower in the Dysbiosis group than in the Control group (4.682 ± 0.236 vs. 6.150 ± 0.361 mmol/L, respectively; $p = 0.002$) (Figure 1C). In addition, serum creatinine concentration was significantly lower in the Dysbiosis group than in the Control group following hemorrhage (0.248 ± 0.012 vs. 0.464 ± 0.064 mg/dL, respectively; $p = 0.01$) (Figure 1E). Collectively, these findings indicate that maternal dysbiosis was associated with a distinct serum electrolyte and renal-related biochemical profile following hemorrhage.

3.3 Maternal Dysbiosis Is Associated with Persistently Higher Calculated Serum Osmolarity

Calculated serum osmolarity was evaluated in animals with complete matched sodium, glucose, and BUN measurements. Two-way ANOVA revealed a significant overall group effect ($p = 0.030$), with calculated serum osmolarity being higher in the Dysbiosis group than in the Control group across both sampling points (306.1 vs. 300.6 mOsm/L; mean difference: 5.565 mOsm/L, 95% CI: 0.730-10.40 mOsm/L). However, neither the main effect of time ($p = 0.65$) nor the time × group interaction ($p = 0.90$) was statistically significant. Calculated serum osmolarity was 301.1 ± 1.4 and 300.1 ± 1.4 mOsm/L before and after hemorrhage, respectively, in the Control group, and 306.4 ± 2.4 and 305.9 ± 2.0 mOsm/L, respectively, in the Dysbiosis group (Figure 1J). These findings indicate that maternal dysbiosis was associated with a consistently higher calculated serum osmolarity, without a significant hemorrhage-induced change.

3.4 Maternal Dysbiosis Is Associated with Organ-Specific Differences in Post-Hemorrhage Wet Weights

Absolute lung wet weight was significantly lower in the Dysbiosis group than in the Control group (1.320 ± 0.044 vs. 1.823 ± 0.099 g, respectively; $p = 0.002$) (Figure 1I). Similarly, absolute brain wet weight was significantly lower in the Dysbiosis group than in the Control group (1.749 ± 0.034 vs. 1.897 ± 0.034 g, respectively; $p = 0.01$) (Figure 1F). In contrast, absolute kidney wet weight did not differ significantly between the Dysbiosis and Control groups (2.189 ± 0.073 vs. 2.120 ± 0.085 g, respectively; $p = 0.55$) (Figure 1G). Absolute heart wet weight was also comparable between the Dysbiosis and Control groups (1.022 ± 0.050 vs. 0.977 ± 0.048 g, respectively; $p = 0.54$) (Figure 1H). These findings indicate that differences in post-hemorrhage wet weights were organ-specific and limited to the lungs and brain.

4. Discussion

The present study provides evidence that maternal and early-life antibiotic-induced dysbiosis is associated with a persistent osmoregulatory vulnerability in offspring, potentially altering the physiological response to acute hemorrhagic stress. While the role of the gut microbiome in modulating chronic immune responses is well established [21,22], its function in fluid dynamics and ionic homeostasis during acute hemorrhagic trauma remains largely undefined. The present findings suggest that the microbial history of the host may modify systemic electrolyte regulation, metabolic adaptation, and organ-specific responses during acute blood loss.

The higher serum sodium and chloride concentrations observed before hemorrhage indicate that dysbiotic offspring entered the experiment with a distinct osmoregulatory profile. This interpretation was supported by the significantly higher calculated serum osmolarity across the two sampling points. However, neither the effect of time nor the time × group interaction was significant, indicating that hemorrhage did not cause an additional increase in calculated osmolarity. Thus, the findings are more consistent with a persistent pre-existing osmotic alteration than with an acute hemorrhage-induced hyperosmolar crisis. Because sodium is the principal determinant of extracellular tonicity, sustained differences in serum sodium may influence fluid distribution between the intracellular and extracellular compartments and modify adaptation to acute blood loss [1].

The gut–kidney axis provides a coherent biological framework for these findings. Gut dysbiosis alters renal physiology through changes in microbial metabolites, uremic toxins, systemic inflammation, sympathetic activity, and the renin–angiotensin–aldosterone system [10-15]. Microbiota-derived short-chain fatty acids, particularly acetate and propionate, are central to this interaction because they activate receptors involved in renal and vascular regulation [24,36]. Olfactory receptor 78 (Olfr78), expressed in the renal juxtaglomerular apparatus, regulates renin secretion in response to short-

chain fatty acids, whereas GPR41/FFAR3 signaling contributes to vascular tone and blood-pressure regulation [24]. Antibiotic-induced disruption of microbial metabolite production can therefore alter the balance between these receptor pathways, renal sodium handling, and neurohormonal compensation. Dysbiosis-associated activation of the intrarenal renin–angiotensin system provides an additional mechanism linking microbial disturbance with sodium retention and elevated calculated osmolarity [15].

The lower BUN and creatinine concentrations identify a metabolic and renal-related response that differs from the conventional prerenal pattern expected during acute volume loss. Both biomarkers are influenced by renal filtration, hepatic urea production, protein catabolism, muscle metabolism, tubular handling, and circulating volume. Their attenuated concentrations, together with persistent sodium and chloride elevations and lower post-hemorrhage potassium, indicate altered coordination of the biochemical mechanisms required to maintain electrolyte and metabolic stability during hemorrhagic stress. Renal sodium transporters and aquaporins are relevant candidates in this response. Hemorrhagic shock has previously been associated with reduced renal expression of AQP2, phosphorylated AQP2, and AQP3 [38], supporting a link between impaired renal water handling and the biochemical phenotype observed in the present model.

The lower lung wet weight was one of the most prominent organ-specific findings. The lung is highly vascularized and responds rapidly to changes in circulating volume, perfusion, extracellular tonicity, and vascular fluid exchange. It is also closely connected to intestinal microbial activity through the gut–lung axis [3,4,20,25,32,33,35]. Gut-derived metabolites regulate pulmonary epithelial integrity, immune function, and vascular homeostasis, whereas intestinal dysbiosis increases pulmonary susceptibility to inflammatory and hemodynamic stress [3,4,20,25]. Broad-spectrum antibiotic exposure can also disturb bacterial-fungal interactions within the intestinal mycobiome, thereby modifying immune communication along the gut-lung axis [26]. The combination of persistently higher calculated serum osmolarity and lower lung wet weight is therefore consistent with increased pulmonary vulnerability to altered fluid distribution during hemorrhage. The absence of comparable reductions in kidney and heart wet weights further indicates that the pulmonary finding was not part of a uniform decrease in organ mass. Although wet weight alone does not establish pulmonary desiccation, this selective pattern supports a biologically relevant interaction between systemic osmotic regulation and pulmonary fluid balance.

The lower brain wet weight is also consistent with the sensitivity of cerebral tissue to changes in extracellular tonicity. The brain depends on tightly regulated water and electrolyte balance, and increased extracellular sodium promotes osmotic movement of water out of neural cells [1]. In addition, communication through the gut-brain, gut-lung, and lung-brain axes involves microbial metabolites, inflammatory mediators, autonomic signaling, vascular responses, and barrier regulation [21-23,27-30]. Disruption of these interconnected pathways can reduce cerebral resilience during systemic stress. Because cerebral adaptation to acute stress is highly dependent on adequate energy homeostasis, disturbances in brain energetics may further impair the capacity to respond to systemic injury [31]. The concurrent reduction in lung and brain wet weights, together with preserved kidney and heart weights, therefore identifies a selective organ pattern involving tissues that depend strongly on barrier integrity, vascular regulation, controlled fluid exchange, and metabolic adaptation.

The unchanged kidney wet weight should not be interpreted as evidence that the kidney was unaffected by dysbiosis or hemorrhagic stress. Renal responses to acute circulatory disturbance are initially driven by changes in perfusion, tubular ion transport, renin–angiotensin system activity, and aquaporin-mediated water handling, all of which can occur without an immediate measurable change in whole-organ mass [15,38]. Accordingly, the coexistence of preserved kidney wet weight with altered BUN, creatinine, sodium, potassium, and calculated serum osmolarity is consistent with a predominantly functional osmoregulatory disturbance rather than gross renal structural loss. Similarly, the unchanged heart wet weight, despite lower lung and brain wet weights, argues against a uniform reduction in the mass of all examined organs. This pattern instead indicates a tissue-selective response, potentially reflecting differences among organs in vascular filling, fluid-exchange capacity, cellular water regulation, and sensitivity to extracellular sodium and tonicity [1,34]. Nevertheless, confirmation of the underlying tissue-level changes requires normalized organ weights and direct structural and hydration measurements.

The main limitations of the study were the absence of molecular confirmation of dysbiosis, direct serum osmolality and tissue water measurements, histological assessment, and body-weight-normalized organ weights.

Future studies incorporating microbiome and short-chain fatty acid analyses, direct osmolality and tissue hydration measurements, histology, aquaporins, renal transporters, and renin–angiotensin–aldosterone system components will help define the underlying mechanisms and determine whether probiotic or metabolite supplementation can reverse the phenotype. Clinically, these findings support closer evaluation of serum sodium and osmolarity in trauma patients with a history of prolonged broad-spectrum antibiotic exposure.

5. Conclusion

In conclusion, maternal and early-life antibiotic-induced dysbiosis was associated with a distinct osmoregulatory and metabolic profile in offspring exposed to hemorrhagic stress. Dysbiotic offspring

exhibited persistently higher serum sodium, chloride, and calculated serum osmolarity, together with altered BUN, creatinine, and potassium responses. Lower absolute lung and brain wet weights, in the absence of comparable changes in kidney and heart weights, further indicated an organ-specific physiological response. Collectively, these findings support a role for the gut microbiota in systemic electrolyte regulation and adaptation to acute blood loss. Clinically, closer monitoring of serum sodium and osmolarity may be relevant in trauma patients with a history of prolonged antibiotic exposure, although this possibility requires confirmation in larger experimental and clinical studies.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval Statement

The study approved by the Bursa Uludağ University Animal Experimentation Local Ethics Committee (Approval No: 2024-03/03) and the study was conducted in accordance with Helsinki Declaration as revised in 2013.

Declaration of Generative AI

The authors confirm that no generative AI technologies were used in the preparation, writing, or data analysis of this manuscript.

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