Обобщающие уроки клинической патофизиологии

СИСТЕМНЫЙ ПОДХОД К ЕСТЕСТВЕННЫМ ПУТЯМ И ВЗАИМОСВЯЗАННЫМ ЗВЕНЬЯМ ПАТОГЕНЕЗА. НАРУШЕНИЙ ВОДНО-ЭЛЕКТРОЛИТНОГО ОБМЕНА. ЧАСТЬ 4. ПАТОФИЗИОЛОГИЯ ЭКСТРЕМАЛЬНЫХ, ТЕРМИНАЛЬНЫХ, НЕОТЛОЖНЫХ, А ТАКЖЕ ИНЫХ СОСТОЯНИЙ, ТРЕБУЮЩИХ ИНТЕНСИВНОЙ ТЕРАПИИ

З. Ковач

Загребский университет, г. Загреб, Хорватия

Integrative Lessons in Clinical Pathophysiology

SYSTEMIC APPROACH TO NATURAL PATHWAYS AND NETWORKING OF ETIOPATHOGENESIS-DISORDERS OF FLUIDS AND ELECTROLYTES. PART FOUR. PATHOPHYSIOLOGY OF EXTREME, TERMINAL, EMERGENCY AND OTHER ICU-STATES

Z. Kovač

Medical School University of Zagreb, Zagreb, Croatia

Резюме. В данном номере мы продолжаем серию материалов по обеспечению самоподготовки по клинической патофизиологии. Форма клинического разбора предполагает активное участие читателей. В соответствии с тематикой данного номера журнала предлагается алгоритмический разбор синдрома гиповолемического шока (часть А). Как этиопатогенетические кластеры (ЭПК) представлены гиповолемия и гемодинамический шок (по 2 клинических разбора) — часть В. Каждый клинический разбор представляет определенную проблему неотложной медицины в контексте конкретного заболевания/нарушения. Решения для задач, как для упражнений от А до С в алгоритмической части, так и для разделов II и III этиопатогенетических кластеров, будут представлены в следующем номере журнала (3 рис., библ.: 8 ист.).

Ключевые слова: водно-электролитный обмен, гиповолемия, гиповолемический шок, диарея, неотложные и экстремальные состояния, холера.

Abstract. In this issue we continue with the series of self-elaborative pathophysiology of clinical problems. The form of study case imposes an active readers' participation. In accordance with the central thematics of this issue the **algorhithmic workout** of hypovolermic shock syndrome is presented (PART A). The **etiopathogenetic clusters (EPC)** of hypovolemia and clinical presentation of hemodynamic shock are illustrated with two case studies in each EPC (PART B). Each study case elaborates the selected emergency problem as the integral context of given disease/disorder.

The solutions of the tasks, both, for A through C exercizes in algorhithmic and for II and III workout segments of EPC-approach, will be provided for a self-control of correct answers in the upcoming issue of the journal (3 figs, bibliography: 8 refs).

Key words: cholera, diarrhea, electrolytes, fluids, hypovolemia, hypovolemic shock, ICU-states.

A) ALGORHITHMIC WORKOUT OF CLINICAL PROBLEM

Pathophysiology of extreme, terminal, emergency and other Intensive Care unit (ICU) states — Pathogenesis of diarrhea in the cholera syndrome[1]

The problem task was based on data from published papers: Fordtran J. S. et al. [2], and Hirst T. R. [3].

A 23-year-old member of a hippy movement on a travel through India got unstoppable diarrhea. Soon after he started vomiting, in half an hour he became apathetic, confused, complained of severe thirst, and became immobile, with "sunken eyes" within orbitae. He was brought to a local hospital. Upon admission he had cyanotic extremities, reduced skin turgor ("dried skin"), arterial blood pressure measuring 70/50 mmHg, pulse of 136 beats per minute, weak central pulse and impalpable pulse of the peripheral arteries. Upon admission, the patient was anuric and soporous. Stool sample was referred to bacteriological diagnostics. After 48 hours, Vibrio cholerae microorganism of El Tor serotype was isolated, by cultivation on selective media containing thiosulfate, citrate, bile salts and sucrose (TCBS-media). During the first three hours of hospitalization, the patient excreted 2600 mL of diarrheic stool, gray-colored, without blood contents and without standard fecal odor. Blood sample

[1] Taken and translated into English from the book Z. Kovač [5] (in Croatian) p. 377–8, with the consent of: the Publisher, Editor and the Author of the case study dr M. Sandrk. Case study code number **19.6** corresponds to the group of processes outlined in the EPC rosette in fig. 2.

indicated increased hematocrit, acidosis and mild hypochloremia. Intravenous infusion of a sterile solution mixture containing 5g NaCl, 4g $NaHCO_3$ and 1 g KCl in 1 liter of distilled water was promptly administered. Simultaneously, tetracycline therapy was initiated. In the beginning, the solution was infused at a speed of 1 L/15 min, until peripheral pulses became palpable and was gradually slowed-down thereafter. With arterial pressure rising, the patient's consciousness improved, so he started taking oral rehydration fluids (according to the recommendation of the World Health Organization, the solution contains 3.5 g NaCl, 2.5 g $NaHCO_3$, 1.5 g KCl and 20 g of glucose in one liter of water). On the fourth day, he started eating solid and mushy food. The patient was discharged on the seventh day of hospitalization. Analysis of electrolyte loss due to diarrhea in the patient with cholera syndrome is shown on fig. 1. Sodium and potassium loss is directly proportional to the volume of secreted diarrhea.

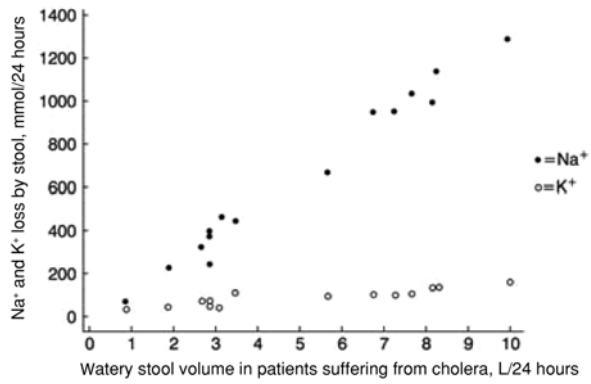

Fig. 1. Relationship between stool volume and electrolyte loss during secretory diarrhea in cholera

Exercise A: Repetitions of relevant knowledge (Circle one correct answer)

1. For the pathogenesis of diarrhea in the cholera syndrome development, all of the following claims are accurate, except:

a) Due to strong activation of the intestinal fluid secretion, the intestine produces a large amount of almost isotonic fluid that causes diarrhea; pathogenetically, this condition is classified as a secretory diarrhea.

b) During Vibrio cholerae infection, which causes clinical features as in the patient, histological changes such as infiltrative colitis can be obtained in the intestinal wall and capillary endothelium.

c) Hyperkalemia is a consequence of acidosis and decreased renal secretion of potassium, and develops regardless of significant potassium loss by the intestinal secretion, where its concentration exceeds the concentration in plasma about three times in quantity (compare fig. 1).

d) Due to dehydration and electrolyte imbalance, skeletal muscle spasms can occur, especially in calves.

e) Sudden appearance of profuse, almost isotonic diarrhea is interpreted as simultaneous activation of epithelial cells over a large intestinal surface, which manifests as profuse secretion of the intestinal fluid.

2. For the molecular pathogenesis of the disease, all of the following statements are true, except:

a) Due to primary loss of plasma oncotic particles (enteropathy with the protein loss), oncodynamic edema and hypovolemic shock can occur in the patient.

b) ADP-ribosylation of the G-protein a-subunit at the position 227 keeps distal biochemical pathways in constantly excited state, which manifests with profuse intestinal fluid secretion.

c) B-subunits of the cholera toxin (choleragen) bind to monosialoganglioside GM1, which serves for A-subunit penetration into the cell, where it catalyzes ADP-ribose transfer from NAD to G-protein, thereby inhibiting.

Ga subunit GTPase activity; G-protein consequently maintains its active state.

d) A1 peptide of the A-subunit of the cholera exotoxin is an enzyme (ADP-ribosyl transferase) which renders a minimal number of toxic molecules sufficient enough for epithelial hypersecretion.

e) Bacteria secrete exotoxin with relative molecular mass of 84 kilodaltons, a thermolabile protein heterodimer composed of A-subunit (which consists of A1 and A2 peptides linked by a disulfide bond) and five B-subunits (homopentamer).

3. Pathogenetic foundation for clinical features as in the patient, can be described by all of the following claims, except:

a) Since watery stools contain two times higher bicarbonate concentration in comparison to plasma levels, this patient developed hypobicarbonatemia and acidosis in plasma.

b) In severe hypovolemia, blood flow decelerates, thereby causing increase in deoxygenated hemoglobin (>50 g/L) which clinically manifests as peripheral cyanosis (see the introduction).

c) Potassium concentration in plasma does not reflect potassium contents within the organism; because after the preliminary hyperkalemia, hypokalemia can occur due to substantial potassium loss through diarrhea (see fig. 1).

d) Cholerigenic effects in epithelial cells do not inhibit glucose nor amino acid absorption from the intestine, which justifies NaCl and glucose supplement to the peroral solution (see the introduction), which can compensate the electrolyte loss.

e) Consciousness impairment in the patient is a direct consequence of toxic choleragen effects on the patient's cerebral cells.

4. Pathogenetically, clinical manifestations of the secretory diarrhea as in the patient, result from all the following mechanisms, except:

a) Since hypovolemia exceeds adaptive capacity of the hemodynamic system, the patient developed circulatory shock of the hypovolemic type (clinical phase of completely expressed circulatory shock syndrome).

b) Activated secretion increases the intestinal fluid volume that induces painless diarrhea; vomiting without nausea can develop as a consequence of antiperistaltic wave activation (compare to the introduction).

c) Achlorhydria, the condition following partial gastric resection, as well as other conditions with decreased gastric acid secretion, contribute to the syndrome development, since smaller quantity of microorganisms is sufficient for the disease development.

d) Physiological gastric acidity reduces the number of Vibrio cholerae bacteria ingested by food approximately by a factor of > 106; pH > 2.4 is no longer protective, while intestinal and biliary fluids contribute to the growth and development (colonization) of that gram-negative bacteria, which through induces the disease through the choleragen secretion.

e) Massive loss of the intestinal contents due to diarrhea causes strong activation of the pancreatic secretion, thus hyperamylasemia and hyperlipasemia could be diagnosed in the patient.

5. Hemodynamic consequences of a strong dehydration of the organism as in the patient, include all of the following mechanisms, except:

a) Tachycardia develops through activation of volume receptors located in the venous system (splanchnic vessels, right atrium) and the arterial receptors located within the arteries (carotid sinus, aortic arch), with homeostatic error signal integration within the vasomotor center located in the hypothalamus.

b) Arterial hypotension, tachycardia, skin pallor and consciousness impairment are clinical indicators of a circulatory shock that developed in the patient due to hypovolemia.

c) In the compensated phase of circulatory shock, there is a strong endocrine system activation, with hypercortisolemia in plasma, increased ACTH, increased renin activity, as well as increased growth hormone concentration.

d) Cholera toxin in the intestinal epithelium and in the intestinal walls decreases blood vessel tonus, thereby pathogenetically categorizing circulatory shock as vasogenic shock.

e) On admission, neither decrease in the venous return, decreased stroke volume nor central venous pressure decrease (the pressure in venae cavae) could be proven as a consequence of hypovolemia in the patient.

Exercise B: Algorhithmic workout of the pathogenesis

Construct the etiopathogenetic algorhithm of the disease by using elements given below:

1. Dehydration of the organism
2. Tachycardia
3. Hypovolemia and hypotension
4. Cholera toxin (choleragen) binding to GM1 in the small intestine epithelium
5. Strong activation of adenylyl-cyclase in the intestinal epithelia
6. Increased hematocrit
7. Skeletal muscle spasms
8. Hypobicarbonatemia
9. Metabolic acidosis (due to base deficit)
10. Profuse secretion of isotonic fluid
11. Rapid loss of extracellular fluid and electrolytes
12. Colonization of the small intestine with Vibrio cholerae microorganism
13. Ingestion of bacteria in contaminated food or water
14. ADP-ribosylation of G-protein a-subunits acquires constantly excited state
15. Uremia and anuria
16. Acute renal failure
17. Strong secretion of Cl^-, Na^+ and water into the intestinal lumen
18. Fluid infusion
19. Impalpable pulse on the peripheral arteries
20. Stool culture proved bacteria after 48 hours
21. Painless, watery and profuse, uncontrollable diarrhea (up to 15 L daily)
22. Strong activation of the volume and pressure receptors
23. Cyanosis
24. Enterocyte protein phosphorylation activates secretory mechanisms
25. Increase in cAMP concentration in the intestinal epithelial cells
26. Impaired consciousness

Exercise C: Feedback integration of the problem (Solve the tasks in following way; Correct claim + correct claim + mutually related = a; correct claim + correct claim + mutually non-related = b; correct claim + incorrect claim = c; incorrect claim + + correct claim = d; inorrect claim + incorrect claim = e)

1. Hypovolemic circulatory shock can develop within 4–12 hours after the start diarrhea, especially when volume of diarrhea exceeds 100 mL/kg/day

because

significant water and electrolyte loss causes hypovolemia which exceeds compensatory capability

of the heart and vessels, thereby causing arterial pressure decrease (claims 4a, 5a and 5b).

a b c d e

2. Inhibition of the G-protein GTP-ase activity by a-subunit ribosylation induces the secretory system in the epithelial cells into a constantly excited state (claims 2b, 2c and 2d)

because

it activates muscarine, vasoactive intestinal polypeptide (VIP) and secretin receptors on the cell membrane.

a b c d e

3. Since G-protein function shift in the patient did not affect glucose nor amino acid transport systems, glucose was added to the peroral rehydration fluid, which enabled sodium-glucose co-transport (see the introduction and claim 3d), with beneficial therapeutic effect

because

this natural absorption pathway of the sodium ensures rehydration of the organism in the time of inhibited GTP-ase activity within the same cells.

a b c d e

Additional questions

4. Name another example of bacterial toxin that has ADP-ribosyl transferase effect, as well as pathogenetic effects on the G-protein function.

5. Calculate the amount of sodium and potassium loss in comparison to their contents in the extracellular space, with stool volume of 8 L/day, according to the data in fig. 1. Calculate osmolality of the intravenously administered fluid as well (see the introduction).

B) THE EPC — WORKOUT OF CLINICAL PROBLEM

Natural tendency of heterogenous etiopathogenetic pathways to influence each other, and to come together are named **etiopathogenetic clusters (EPC)**. Analysis and consideration of such clustering points are important for understanding of the nature of disease. The EPCs are important networking elements in biological reactivity. In fig. 2 and 3 the EPC-rosettes outline various groups of diseases/conditions and their etiologies — which form the same ECP. **The EPC of Hypovolemia** and **the EPC of Hypovolemic shock**, are presnted. The rosettes are followed by **two case studies** within the each EPC.

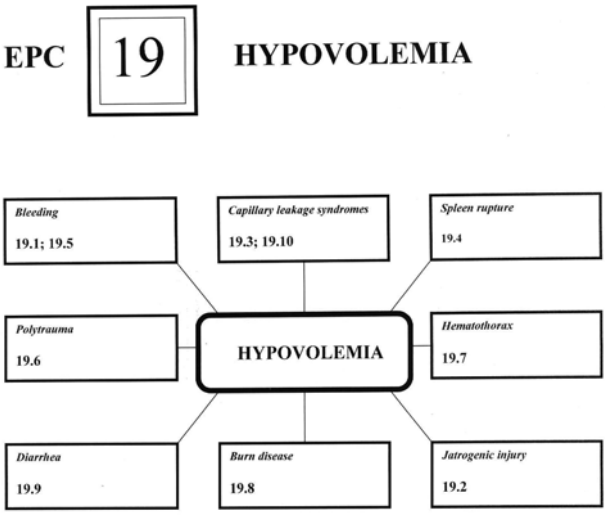

Fig. 2. Introductory rosette of (EPC) of hypvolemia serves as navigation scheme among multiple groups conditions, all related to this electrolyte disorder. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book

CASE STUDY 19.6. HYPOVOLEMIA — WITH HYPOVOLEMIC SHOCK, HEAD CONTUSION, PNEMOTHORAX AND INTERNAL BLEEDING IN PATIENT WITH POLYTRAUMA[2]

The case study has been adopted from the article of Iida K. et al. [7].

I. **Medical history.** A 20-year-old man was transferred to the Department of Neurosurgery for the treatment of multiple injuries resulting from a traffic accident. According to the Glasgow coma scale disturbance of consciousness was 7/15, (3/15 indicates deep coma, 15/15 means complete mental alertness and awareness), and had a tachycardia of 127 beats/min (normal range 60–80), and arterial hypotension of 70/37 mm Hg (normal range 90–135/60–85). In addition to disturbed consciousness, he had hematomas on his face and head, and abdominal distension. The laboratory tests revealed hypohemoglobinaemia (64 g/L, normal range 120–160) and decreased hematocrit (0.200, normal range of 0.370 to 0.500). Tomograms (CT, Computed Tomography) of the thorax revealed contusion and pneumothorax, and the CT scans of abdomen contusions of the liver parenchyma and hemoperitoneum. Cranial CT scans were normal. Transcranial Doppler sonography (TSD) showed a disturbed cerebral hemodynamics.

Clinical picture and diagnostic findings revealed hypovolemia, caused by bleeding into the abdominal cavity. An emergency laparotomy was made, and liver

[2] Taken and translated into English from the book Z. Kovač [5] 2013 (in Croatian) p. 375–6, with the consent of the Publisher, Editor and the Author of the case study dr D. Grebic. Case study code number **19.4** corresponds to the group of processes outlined in the EPC rosette in fig. 2.

injury with hemorrhage into the abdominal cavity was found, and blood transfusion was applied. The patient was discharged after two months, with minimal neurological sequelae.

ADDITIONAL INSIGHT: Hypovolemic shock in patient is the result of internal bleeding caused by a polytraumatic hematomas of lung and liver tissue. Reduced arteriovenous pressure difference excites the pressure and volume receptors, which causes the sympathetic and endocrine response, and consequently, the centralization of the blood flow. Hypotension and tachycardia are the result of the above. Moreover, in hypovolemia and decreased tissue flow hypoenergosis develops (hypoxic substrate), which in this patient clinically was presented as a disturbed consciousness.

Hypohemoglobinaemia and reduced hematocrit in a patient are due to blood dilution due to the entry of fluid from the capillaries to the interstice, thus compensating the reduction in blood volume.

Transcranial Doppler (TCD) sonography is a noninvasive, ultrasound diagnostic method, which provides insight into the intracranial vertebrobasilar and carotid circulation. These arteries create an anastomosis on the base of the brain forming a circle of Willis, and are responsible for the normal supply of the brain and thus, its function. TCD is used for diagnosis and monitoring of head injuries, subarachnoidal bleeding and blood vessel diseases of the brain.

The Glasgow coma scale includes three tests: eye, verbal and motor response, which examines the objective state of mind of the patient. The three values separately as well as their grades are added together. The smallest possible sum is 3, and indicates a deep coma, while the highest value of 15, and marks the complete mental alertness.

II. **Etiopathogenesis of the disease.** (Using the given elements compose an etiopathogenetic algorithm of the disease)

1. Tachycardia
2. Reducing an arteriovenous pressure difference
3. Disturbance of consciousness
4. Anemia
5. Centralization of the circulation
6. Dispatch vasomotoric center
7. Acute bleeding
8. Reducing the flow through the tissue and tissue hypoenergosis

III. **Classification of etiopathogenetic nature and development of disease/disorder/condition.** According to data presented in this case study please outline a) 5 etiological features; b) 18 features of pathogenesis; c) 16 features of disease spread and chronobiology; d) 10 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS*** specified on page 132 of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable.

CASE STUDY 19.4. HYPOVOLEMIA — DUE TO PERITONEAL BLEEDING WITH SHOCK AND DEATH WITHIN SPONTANEOUS SPLENIC RUPTURE IN INFECTIOUS MONONUCLEOSIS[3]

The case study has been adopted from the article of Birkinshaw R. et al. [1].

I. **Medical History**: A 15-year-old female complained about fever, difficult swallowing and generally feeling unwell. Physical examination revealed cervical lymphadenopathy, an increase in the palatal tonsils with pharyngitis. Abdominal palpation revealed splenomegaly. She was diagnosed with infectious mononucleosis (positive Paul-Bunnell test). The patient received the non-steroidal antirheumatic drugs to relieve symptoms and reduce fever.

Four days later she complained about abdominal pain. The next day, abdominal pain was still present, but tachycardia and arterial hypotension developed. Arterial pressure was 50 mmHg (normal range 100–140/60–90), pulse 170/min (normal range 60–100), oxygen saturation measured by pulse oximeter 97% (normal range 95–100). Soon after admission, the patient had a cardiopulmonary arrest. The initial lethal rhythm was ventricular fibrillation. Cardiopulmonary resuscitation was performed, with defibrillation. Blood replenishment was immediately started as well, along with the use of colloidal solution. During resuscitation, fibrillation turned into asystole. The patient received atropine (anticholinergic). After 45 minutes of cardiopulmonary resuscitation, along with the use of drugs and replenishment of lost blood, status remained unchanged, and the patient died. Autopsy revealed rupture of the spleen, whose dimensions were about six times greater than normal. The patient had massive intraperitoneal hemorrhage.

Additional Insight: Infectious mononucleosis is a contagious viral disease caused by Epstein-Barr virus (belongs to the herpes viruses), which is transmitted through aerosols. It manifests as tonsillopharyngitis, cervical lymphadenopathy, fever, and splenomegaly. The course is benign, requiring only symptomatic treatment. The most serious complication which may occur as a result of this disease is splenic rupture, and

[3] Taken and translated into English from the book Z. Kovač [5] 2013 (in Croatian) p. 375–6, with the consent of the Publisher, Editor and the Author of the case study dr D. Grebic. Case study code number 19.4 corresponds to the group of processes outlined in the EPC rosette in fig. 2.

is manifested as abdominal pain, sometimes palpably hard abdominal wall, and signs of hemorrhagic, hypovolemic shock (arterial hypotension, tachycardia, pale skin, cold sweat, weak pulse, oliguria).

The diagnostic method of choice for the detection of splenomegaly as well as splenic rupture with consequential hemorrhage in the peritoneal cavity is ultrasound. A diagnostic test for infectious mononucleosis is the Paul-Bunnell test (presence of antibodies in the blood of patients who agglutinate erythrocytes *in vitro*).

II. **Etiopathogenesis of the disease.** (Using the given elements compose an etiopathogenetic algorithm of the disease).

1. Intraperitoneal hemorrhage
2. Splenic rupture
3. Infectious mononucleosis
4. Tonsillopharyngitis
5. Fever
6. Tachycardia
7. Splenomegaly
8. Arterial hypotension

III. **Classification of etiopathogenetic nature and development of disease/disorder/condition.** According to data presented in this case study please outline a) 5 etiological features; b) 14 features of pathogenesis; c) 9 features of disease spread and chronobiology; d) 12 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS*** specified on page 132 of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable.

CASE STUDY 52.2. HYPOVOLEMIC SHOCK — WITH HEMATEMESIS AND CARDIAC ARREST AFTER PARTIAL GASTRECTOMY[4]

The case study has been adopted from the article of Sharma R. M. et al. [8].

I. **Medical history.** In a 53-year old man with gastric cancer, the lower part of the stomach and the neck of the pancreas were surgically removed. The connection of the small intestine with stomach and with pancreas were made, respectively. There were no disturbances in the early period after the surgery. The seventh postoperative day he began bleeding heavily and vomited 2 L of blood (hematemesis). He lost consciousness. During the endotracheal intubation, the patient's heart stopped beating (cardiac arrest). The heart rhythm was restored by defibrillation and bleeding was tried to stop operatively. During the procedure the patient was hypotensive and he experienced a cardiac arrest again. Cardiac resuscitation, application of norepinephrine and dobutamine, fluid replacement, blood transfusion and fresh frozen plasma were applied.

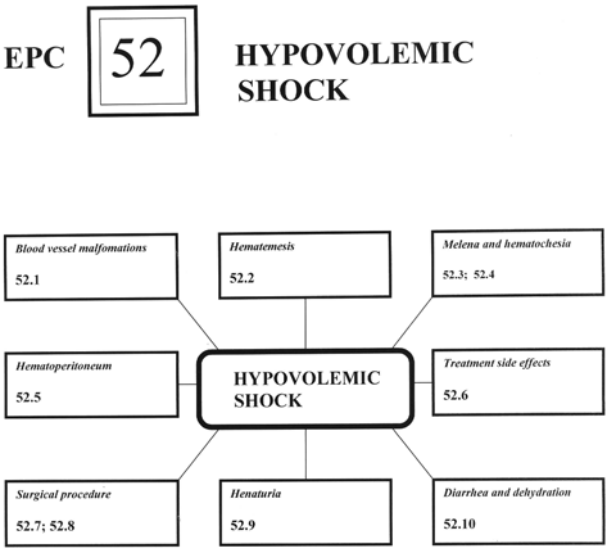

Fig. 3. Introductory rosette of (EPC) of hypovolemic shock syndomes serves as navigation scheme among multiple groups conditions, all related to this electrolyte disorder. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book

The bleeding stopped after two hours. Central venous pressure was 0.98 kPa (normal range 0.1–0.3) after infusion of total 13 L of crystalloids and 1 L of colloids, 1 L of fresh frozen plasma and an transfusion of 5 L of blood. Arterial pressure was 10.66/6.66 kPa (normal range 8–13.3/16–18.6). Five hours from the beginning of the surgery vasopressin was instituted and arterial blood pressure increased to 14.66/9.33 kPa 30 min thereafter. However, severe metabolic acidosis, pH 7.1 (normal range 7.4 $\pm$ 0.02) with base deficit of –11.4 (normal range 0 $\pm$ 2) was not corrected. Therefore, artificial ventilation and infusion of sodium bicarbonate to correct the base deficit were continued. The patient was transferred to the intensive care unit, where his mean arterial pressure was 8.66 kPa. Vasopressin and norepinephrine were gradually removed from the treatment after 24 and 48 hours, respectively. The patient became hemodynamically stable.

ADDITIONAL INSIGHT: In decompensated stage of hypovolemic shock cardiac arrest in diastole is due to toxic effects of acidosis on myocardium and hyperkinetic loading rate due to a decrease in total peripheral resistance (vasodilatation), caused by release of adenosine, K^+ and H^+ ions, and CO_2, NO, cAMP and cGTP from ischemic cells. Treatment by volume replacement and catecholamine is usually insufficient

[4] Taken and translated into English from the book Z. Kovač [5] (in Croatian) p. 1278–9, with the consent of the Publisher, Editor and the Author of the case study dr G. Laskarin. Case study code number **52.2** corresponds to the group of processes outlined in the EPC rosette in fig. 3.

for a longer duration hypovolemia. Additional application of vasopressin (ADH) increases blood pressure by water reabsorption in distal convoluted tubule and collecting ducts of kidneys, and by vasoconstrictive actions. Vasopressin decreases vasodilatation by inhibiting release of K^+ from cells through potassium channels. It also reduces vasodilatation by preventing NO caused accumulation of cGMP in intercellular space.

II. **Etiopathogenesis of the disease.** (Using the given elements compose an etiopathogenetic algorhithm of the disease.)

1. Hypovolemia
2. Decrease in cardiac contractility until cardiac arrest
3. Stopping blood flow
4. Hypoxia
5. Hypoenergosis
6. Acidosis
7. Bleeding in the area of surgery and hemathemesis
8. Vasopressin treatment, blood transfusion, fresh frozen plasma and pH adjustment

III. **Classification of etiopathogenetic nature and development of disease/disorder/condition.** According to data presented in this case study please outline a) 4 etiological features; b) 18 features of pathogenesis; c) 7 features of disease spread and chronobiology; d) 10 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS*** specified on page 132 of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable.

CASE STUDY 52.9. HYPOVOLEMIC SHOCK — WITH HYPOHEMOGLOBINEMIA AND SYNCOPE BECAUSE OF BLEEDING FROM THE URINARY TRACT, CAUSED BY AN INFLAMMATORY PSEUDOTUMOR OF THE URINAL BLADDER[5]

The case study has been adopted from the article of Lantz A. G. et al. [6].

I. **Medical history.** A 44-year-old woman was admitted to the emergency room because of dysuria (during the last 3 weeks) and macrohematuria (in the last 5 days), followed by urinating blood clots the last night before the admission. The patient was previously treated because of a suspect urinary tract infection, but the urine culture result came back negative. Her physical status, biochemical lab results, blood count and coagulation tests showed nothing out of order [(pulse 88/min (normal 60–100), respiration rate 14/min (normal 12–16), blood pressure 112/72 mmHg (normal 100/60 do 130/85), blood creatinine level 58 μmol/L (normal 53–106), hemoglobin level 125 g/L (normal 120–160)]. Urine analysis showed the presence of blood and proteinuria 2+ (2+ has a standard meaning I medicine, just live it as it is). The patient was released with a recommendation for treatment in the Urological clinic.

The next day, the patient came back to the hospital because of vertigo, weakness and persistent hematuria. She had an episode of syncope and vomiting at home, and was complaining about frequent urination and a pronounced urge to urinate. She was afebrile but tachycardic (pulse 102 per minute), with respiration rate 16/min, and BP 128/84 mmHg. The patient was pale and had dry skin. The abdomen was palpatory soft. Lab results showed negative beta-human chorion gonadotropin, leukocytosis (13.7×10^9/L, normal 3.4–9.7), hypohemoglobinemia (Hb 102 g/L), increase of the creatinine level (in comparison to former values) up to 99 μmol/L; urea 5.1 mmol/L (normal 2.5–6.4). She was treated with intravenous rehydration. The blood type was soon determined. Continuous irrigation of the urinal blather started, but the hematuria persisted. After the i. v. rehydration, the hemoglobin level was 66 g/L, pulse 108/min, respiration rate 22/min. Blood pressure was 106/66 mmHg.

Tomogram of the abdomen and the pelvis showed a tumor, growing from the front wall of the urinal blather (4.3 cm × 3.5 cm). There was no proof of the penetration of the tumor outside the urinal blather, as well as no metastatic changes in the abdomen and pelvis have been found. Cystoscopy showed a tumor growing from the wall of the urinal blather. A transurethral resection of the tumor has been made, and the patient received erythrocyte transfusion during the operation. Two days after, the patient was released home, with a planned repeated resection in two week time. But the next morning, the patient came back to the hospital because of general weakness, vertigo and hematuria. Her lab results showed hemoglobin level decrease, 88 g/L. Blood clots were removed, and a repeated resection was done, as well as fuguration (destruction of the tumor using electric power). Patohystological analysis of the tumor showed proliferation of the spindle-shaped cells, with no proof of malign transformation or high degree dysplasia. After the imunohystochemical analysis result, a diagnosis of atypical pseudo sarcomatic miofibroblastic proliferation of the urinal blather, that is, inflammatory pseudotumor, was established. A partial cistectomy has been made. The patient felt good after the operation, and had no signs of hematuria.

ADDITIONAL INSIGHT: An inflammatory pseudotumor of the urinary blather is also known as:

[5] Taken and translated into English from the book Z. Kovač [5] (in Croatian) p. 1287–8, with the consent of the Publisher, Editor and the Author of the case study dr M. Sirotkovic Skerlev. Case study code number **52.9** corresponds to the group of processes outlined in the EPC rosette in fig. 3.

pseudo-sarkomatic miofibroblastic proliferation, pseudo malign proliferation of the spindle-shaped cells, pseudo sarcoma, nodular fasciitis of the urinary blather, and a reactive pseudo sarcoma response. IPT is a rare and benign lesion of the urinary blather which can result with a life-threatening situation. In the case of this patient, massive and persistent hematurias lead to a clinically significant hypovolemia and a border shock disorder. The bleeding, gradual deterioration of the hypohemoglobinemia, arterial hypotension followed by tachycardia, as well as neurological symptoms suggest that the patient's hemodynamic state was on a border between compensated and decompensated shock.

Hypovolemic shock is a type of shock that develops because of the loss of such amount of blood that exceeds the adjustment capacity of the circulatory system. It can be caused by bleeding, plasma loss or loss of water and electrolytes from the extracellular compartment.

In order to distinguish IPT from similar malign tumors, a detailed patohystological analysis with corresponding imunohystochemical analysis is needed. Therapy consists of transurethral resection and partial cystectomy. Radical cystectomy is not an option, since IPT is a benign lesion.

II. **Etiopathogenesis of the disease.** (Using the given elements compose an etiopathogenetic algorhithm of the disease)

1. Hematuria
2. Inflammatory pseudotumor (IPT)
3. Hypovolemia and a decrease in the arteriovenosus pressure difference
4. Tachycardia
5. Pale skin
6. Hypohemoglobinemia
7. Therapy: i. v. rehydration, transurethral tumor resection, partial cystectomy
8. Syncope

III. **Classification of etiopathogenetic nature and development of disease/disorder/condition.** According to data presented in this case study please outline a) 2 etiological features; b) 11 features of pathogenesis; c) 5 features of disease spread and chronobiology; d) 11 features of clinical elaboration (diagnosis, therapy) — using the ***CLASSIFICATION AND DISAMBIGUATION ELEMENTS*** specified on page 132 of this issue. Only the features which come out of presented medical history and etiopathogenetic elaboration of processes are acceptable.

БИБЛИОГРАФИЯ

1. *Birkinshaw R., Saab M., Gray A.* Spontaneous splenic rupture: an unusual cause of hypovolaemia. J. Accid. Emerg. Med. 1996; 13: 289–91.
2. *Fordtran J. S., Dietschy J. M.* Water and electrolyte movement in the intestine. Gastroenterology. 1966; 50: 263–85.
3. *Hirst T. R.* Conformation of the protein secreted across bacterial outer membranes: A study of enterotoxin translocation from vibrio cholerae. Proc. Natl. Acad. Sci. USA. 1987; 74: 7418–22.
4. *Kovač Z., Gamulin S.,* ed. Pathophysiology. Study Guide Algorhithms — Problem Solver. Book Two. Zagreb: Medicinska Naklada; 2013. (In Croatian)
5. *Kovač Z.* Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One. Zagreb: Medicinska Naklada; 2013. (In Croatian)
6. *Lantz A. G., Power N. E., Gupta R., Grantmyre J.* Inflammatory pseudotumor: a rare cause of hematuria and shock. Urology. 2007; 70: 3–6.
7. *Iida K., Kurisu K., Arita K., Nakahara T., Ohtani M., Satoh H.* Evaluation of cerebral hemodynamics in a headinjured patient with hypovolemia using transcranial doppler sonography. Am. J. Emerg. Med. 1997; 5: 587–90.
8. *Sharma R. M., Setlur R.* Vasopressin in hemorrhagic shock. Anesth. Analg. 2005; 101: 833–4.

REFERENCES

1. *Birkinshaw R., Saab M., Gray A.* Spontaneous splenic rupture: an unusual cause of hypovolaemia. J. Accid. Emerg. Med. 1996; 13: 289–91.
2. *Fordtran J. S., Dietschy J. M.* Water and electrolyte movement in the intestine. Gastroenterology. 1966; 50: 263–85.
3. *Hirst T. R.* Conformation of the protein secreted across bacterial outer membranes: A study of enterotoxin translocation from vibrio cholerae. Proc. Natl. Acad. Sci. USA. 1987; 74: 7418–22.
4. *Kovač Z., Gamulin S.,* ed. Pathophysiology. Study Guide Algorhithms — Problem Solver. Book Two. Zagreb: Medicinska Naklada; 2013. (In Croatian)
5. *Kovač Z.* Clinical Pathophysiology. Etiopathogenetic Clusters. Book Three. Part One. Zagreb: Medicinska Naklada; 2013. (In Croatian)
6. *Lantz A. G., Power N. E., Gupta R., Grantmyre J.* Inflammatory pseudotumor: a rare cause of hematuria and shock. Urology. 2007; 70: 3–6.
7. *Iida K., Kurisu K., Arita K., Nakahara T., Ohtani M., Satoh H.* Evaluation of cerebral hemodynamics in a headinjured patient with hypovolemia using transcranial doppler sonography. Am. J. Emerg. Med. 1997; 5: 587–90.
8. *Sharma R. M., Setlur R.* Vasopressin in hemorrhagic shock. Anesth. Analg. 2005; 101: 833–4.

УВЕДОМЛЕНИЕ

Автор заявляет об отсутствии конфликта интересов применительно к публикации данной статьи. Вся работа выполнена одним автором.

СВЕДЕНИЯ ОБ АВТОРЕ

Ковач Зденко — профессор, кафедра патофизиологии, медицинский факультет, Загребский университет, Госпитальный центр КВС, Хорватия, Загреб, Кишпатичева ул., д. 12, e-mail: zdenko.kovac@mef.hr

ACKNOWLEDGEMENT

The author declare no conflict of interest in relation to the publication of this article. All work is done by one author.

INFORMATION ABOUT AUTHOR

Kovač Zdenko — professor, Department of Pathophysiology, Medical School University of Zagreb, KBC-Hospital Centre, Kišpatićeva 12, Zagreb Croatia, e-mail: zdenko.kovac@mef.hr

Z. Kovač. Integrative Lessons in Clinical Pathophysiology:

CLASSIFICATION AND DISAMBIGUATION OF ETIOPATHOGENETIC CHARACTER AND COURSE OF DISEASE PRESENTED IN THE EPC CASE STUDY — ELEMENTS

a) Etiological characteristics of a patient's condition.

1. **Biological etiology**; 1.1 genetic, 1.2 monogenic, 1.3 polygenic, 1.4 infectious, 1.5 bacterial, 1.6 viral, 1.7 plasmodial, 1.8 infestive, 1.9 parasitic, 1.10 fungal, 1.11 transplant reaction, 1.12 developmental anomaly, 1.13 fetomaternal unit disorder

2. **Physical etiology**; 2.1 mechanic, 2.2 trauma, 2.3 hypoosmolar, 2.4 hyperosmolar, 2.5 hyperhydration, 2.6 hypohydration, 2.7 hypovolemic, 2.8 oncotic, 2.9 burn injury, 2.10 hyperthermia, 2.11 hypothermia, 2.12 electrical injury, 2.13 ultrasound, 2.14 vibration, 2.15 obstructive, 2.16 overload, 2.17 hyperviscous, 2.18 deceleration, 2.19 acceleration, 2.20 acoustic, 2.21 hydrostatic, 2.22 decreased tissue elasticity, 2.23 environmental pressure change, 2.24 immobilization, 2.25 radiation

3. **Chemical etiology**; 3.1 intoxication, 3.2 hypovitaminosis, 3.3 hypervitaminosis, 3.4 corrosive, 3.5 biological poisoning (insects, snakes, mushrooms, marine organisms etc.), 3.6 xenobiotics, 3.7 drug overdose, 3.8 endogenous metabolite accumulation, 3.9 carbohydrate disorder, 3.10 protein disorder, 3.11 lipid disorder

4. **According to etiopathogenesis**; 4.1 endogenous, 4.2 exogenous, 4.3 iatrogenic, 4.4 medicamentous, 4.5 professional, 4.6 malnutrition, 4.7 lifestyle-related, 4.8 smoker, 4.9 addiction, 4.10 suicidal, 4.11 accidental, 4.12 deficiency of basic metabolic substances, 4.13 deficiency of specific metabolic substances, 4.14 congenital, 4.15 spontaneous, 4.16 explosive, 4.17 induced, 4.18 alcohol abuse

b) Characteristics of pathogenesis, natural course, degree of dysfunction and outcome of a disease.

5. **Characteristics of pathogenetic character of a process**; 5.1 inflammatory, 5.2 neoplastic, 5.3 ischemic, 5.4 metabolic, 5.5 autoimmune, 5.6 immunodeficiency, 5.7 alloreactivity, 5.8 atopic, 5.9 allergic, 5.10 anaphylactic, 5.11 anabolic, 5.12 catabolic, 5.13 degenerative, 5.14 electrolyte disorder, 5.15 acid-base disorder, 5.16 hypoenergosis, 5.17 substrate deficiency, 5.18 dysenzymatic, 5.19 glycation, 5.20 hypoglycemic, 5.21 hyperglycemic, 5.22 dyslipidemia, 5.23 hypoxemia, 5.24 hypoxia, 5.25 carbonylation, 5.26 methylation, 5.27 dysregulatory, 5.28 hypertensive, 5.29 hypotensive, 5.30 spastic-paralytic, 5.31 channelopathy, 5.32 hypothermic, 5.33 hyperthermic, 5.34 fibrosis, 5.35 maldigestion, 5.36 malabsorption, 5.37 hemorrhagic, 5.38 protein-loss, 5.39 necrotic, 5.40 apoptotic, 5.41 atherosclerotic, 5.42 arrhythmogenic, 5.43 epileptogenic, 5.44 edema, 5.45 infiltrative, 5.46 granulation, 5.47 tetanic, 5.48 acidotic, 5.49 alkalotic, 5.50 amyloidotic, 5.51 DNA repair disorder, 5.52 translation disorder, 5.53 excitotoxicity, 5.54 oxyfority disorder, 5.55 coagulopathy, 5.56 mitochondrial dysfunction, 5.57 lysosomal disorder, 5.58 membranous dysfunction, 5.59 proliferation, 5.60 endoplasmic reticulum disorder, 5.61 shock, 5.62 acute stress, 5.62 chronic stress, 5.64 compartmentalisation, 5.65 septic, 5.66 hypertrophic, 5.67 tamponade, 5.68 hypoproteinemic, 5.69 cachectic, 5.70 hemolytic, 5.71 hypermetabolic, 5.72 hypometabolic, 5.73 receptor dysfunction, 5.74 neoangiogenic, 5.75 tesaurismosis, 5.76 reduced catabolism of self molecules, 5.77 thrombogenic, 5.78 hypercytokinemia, 5.79 tissue transplant reaction, 5.80 flaccid paralysis, 5.81 asfixia, 5.82 hyperventilation, 5.83 hypoventilation, 5.84 hypercapnia, 5.85 hypocapnia, 5.86 embolic

6. **Characteristics according to disease course**; 6.1 irreversible, 6.2 reversible, 6.3 progressive, 6.4 remission, 6.5 acute, 6.6 subacute, 6.7 chronic, 6.8 fulminant, 6.9 primary, 6.10 secondary, 6.11 n-th pathogenesis, 6.12 subclinical

7. **Characteristics according to the degree of dysfunction and disease outcome**; 7.1 compensated, 7.2 decompensated, 7.3 latent insufficiency, 7.4 manifest insufficiency, 7.5 hyperreactivity, 7.6 hyporeactivity, 7.7 afunction, 7.8 moribund, 7.9 terminal, 7.10 urgent condition, 7.11 intensive-care, 7.12 elective treatment, 7.13 vegetation state, 7.14 lethal, 7.15 vital threat

c) Characteristics of disorder staging and chronobiology of a patient.

8. **Characteristics based on process dissemination in organs, tissues, compartments and body fluids**; 8.1 cutaneous, 8.2 osseus, 8.3 articular, 8.4 cerebral, 8.5 vascular, 8.6 venous, 8.7 arterial, 8.8 interstitial, 8.9 intracellular, 8.10 pulmonary, 8.11 bronchial, 8.12 diaphragmal, 8.13 neural, 8.14 intestinal, 8.15 hepatic, 8.16 biliary, 8.17 pancreatic, 8.18 muscular, 8.19 cardiac, 8.20 epithelial, 8.21 hematologic, 8.22 lymphatic, 8.23 cerebrospinal, 8.24 mammary, 8.25 utero-vaginal, 8.26 penile-testicular, 8.27 abdominal, 8.28 renal, 8.29 vesico-ureteral, 8.30 extracellular, 8.31 ascitic, 8.32 mono-organic, 8.33 multi-organ, 8.34 pleural, 8.35 with integral affection of specific body parts (foot, leg, arm, eye, ear, throat, nose, neck, mediastinum etc.), 8.36 pericardial, 8.37 tracheal, 8.38 capillary, 8.39 prostatic

9. **Characteristics according to the population affected**; 9.1 epidemic, 9.2 infectious, 9.3 pandemic, 9.4 endemic, 9.5 familial

10. **Characteristics according to functional system affection**; 10.1 hemodynamic, 10.2 respiratory, 10.3 thermoregulatory, 10.4 endocrine, 10.5 neurovegetative, 10.6 immune, 10.7 renal-urinary, 10.8 hematological, 10.9 locomotor, 10.10 genital-reproductive, 10.11 osseous-connective tissue, 10.12 peripheral sensory disorder, 10.13 peripheral motor disorder, 10.14 central nervous system disorder, 10.15 gastrointestinal

11. **Chronobiological characteristics of a patient**; 11.1 embrional, 11.2 fetal, 11.3 neonatal, 11.4 developmental, 11.5 childhood, 11.6 adolescent, 11.7 opstetric, 11.8 reproductive, 11.9 postmenopausal, 11.10 adult, 11.11 geriatric, 11.12 fertilization disorder

d) Characteristics of clinical diagnostics and treatment modalities.

12. **Characteristics of diagnostic and therapeutic interventions**; 12.1 anamnestic, 12.2 physical-examination, 12.3 laboratory, 12.4 imaging modalities, 12.5 dynamic tests, 12.6 endoscopic, 12.7 stereotactic, 12.8 ultrasound, 12.9 radionuclide, 12.10 molecular, 12.11 pathohystological, 12.12 pathoanatomical, 12.13 cytological, 12.14 genetic analysis, 12.15 symptomatic, 12.16 causal, 12.17 curative, 12.18 palliative, 12.19 conservative, 12.20 medicamentous, 12.21 operative, 12.22 cytostatic, 12.23 antibiotic, 12.24 immunosuppressive, 12.25 substitution, 12.26 diuretic, 12.27 cardiotonic, 12.28 functional x-ray imaging, 12.29 invasive, 12.30 fine needle aspiration, 12.31 tissue transplant, 12.32 autopsy, 12.33 anesthesia, 12.34 transfusion, 12.35 fluid replenishment, 12.36 hypolipemic, 12.37 immunostimulatory, 12.38 antihypertensive, 12.39 antiepileptic, 12.40 antidepressive, 12.41 sympathomimetic, 12.42 sympatholytic, 12.43 parasympathomimetic, 12.44 parasympatholytic, 12.45 antiemetic, 12.46 radiotherapy, 12.47 antipyretic, 12.48 anti-inflammatory, 12.49 with euphenic diet, 12.50 hemodialysis, 12.51 peritoneal dialysis, 12.52 plasmapheresis, 12.53 biological therapy (humanized antibodies, recombinant proteins etc.), 12.54 desensibilization, 12.55 anticoagulant treatment