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## **Parenteral feeding complications in pediatrics**

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*The article is dedicated to parenteral feeding – infusion therapy aimed at introducing water, macro- and micronutrients in concordance with body needs. Different parenteral feeding types are described: complete, partial and additional. It shows that balanced parenteral feeding allows providing the child's body with the sufficient amount of amino acids, carbohydrates, fats and energy required to maintain a baseline energy level and correct a preceding nutritive insufficiency. Protein-energy homeostasis is the basis for vital activity of the body; it determines the inflammatory response activity, immune status adequacy, disease duration and severity and disease prognosis (to a considerable degree). Long-term parenteral feeding is associated with complications of varying severity: from transitory and mild to severe, requiring operative intervention and liver transplantation. The command of modern recommendations allows a practicing doctor to successfully overcome issues associated with long-term parenteral feeding. The article presents modern data on diagnostics, prevention and treatment of parenteral feeding complications.*

**Keywords:** parenteral feeding, complications, children, infusion therapy, nutrients.

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Balanced wholesome nutrition is the basis of harmonious growth and development of children. Unlike adults, children require adequate nourishment not only for supporting vital activity of the body, but also for growth, which is especially important for infants and adolescents.

Nutritive insufficiency caused by the lack of or limited facilities of the gastrointestinal tract in terms of intake, digestion and/or reabsorption of nutrients indicates the parenteral feeding (PF).

The PF is the infusion therapy aimed at introducing water, macro- and micronutrients in concordance with body needs.

There is complete, partial and additional PF. Partial/mixed PF is the parenteral introduction of nutrients in case the enteral introduction facilities are limited. Additional PF is the introduction of singular nutrients in order to increase the need in them (e.g., additional prescription of amino acids in case there is a need in activating reparative processes).

2 PF types are distinguished according to the venous access type:

- peripheral PF – not more than 2 weeks using not more 10%-glucose solutions;
- central PF – in case peripheral access is restricted and PF duration for more than 2 weeks using more than 10%-glucose solutions [1].

Long-term complete PF is associated with the development of a wide range of complications of varying severity. PF complications are caused by the following factors [2]:

- central venous catheter (CVC);
- instability of PF solutions;
- interaction between the introduced solutions and pharmacological drugs;
- metabolic disorders.

### **Complications associated with central venous catheter**

#### ***Infectious complications.***

Infection is one of the most widespread causes of complications associated with CVC; it is associated with the reduction in survivability parameters at resuscitation and intensive therapy units. Observation of aseptic and antiseptic rules serves as the basis for preventing infectious complications. It is well-known that “horizontal” infection transmission route may be the primary in the development of purulent-septic complications. Thus, preparation of PF solutions, assembly and connection of infusion lines to CVC should take place in aseptic conditions with obligatory use of sterile gloves. It must be noted that dextrose (glucose) and amino acid solutions at PF should be replaced at least once in 72 hours, fat emulsions – at least once in 24 hours.

When conducting PF, it is necessary to check for the catheter-related sepsis every day. Development of such clinical signs as fever (body temperature over 38.0°C), metabolic acidosis, thrombocytopenia or unstable blood glucose content in a child may indicate an infectious process. In case the listed symptoms are revealed, the CVC blood culture must be conducted immediately. According to the recommendations of the International organization “The Surviving Sepsis Campaign” (SSC), the CVC and peripheral venous blood and other biologic fluids, which may serve as infection source, must be sampled for cultural studies before the anti-infectious therapy [3]. According to the literary data, gram-positive bacteria – staphylococci and enterococci are the most frequent causative agents of catheter-related bloodstream infections;

genus *Enterobacteriaceae* microbes are far rarer. Non-fermentative bacteria (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*) and yeast-like fungi are relatively rare, however, the infections they cause have unfavorable course [4].

We conducted a retrospective analysis of the own data: cultural bacteriologic studies of the CVC blood samples in 93 children taken from 01.04.2012 to 01.04.2013. We revealed that growth was taking place in 41 (10.76%) out of 381 presented samples. The most frequently growing bacteria were *Staphylococcus epidermidis* (16 cases – 39.2%), *Klebsiella pneumonia* (5 cases – 12.19%), *Leuconostoc lactis* (2 cases – 4.87%), *Acinetobacter baumannii* (2 cases – 4.87%); other bacterial causative agents were revealed in 6 more cases. Genus *Candida* yeast-like fungi were revealed in 11 samples: *Candida parapsilosis* – in 9 cases (21.95%), *Candida glabrata* and *Candida albicans* – in 1 case (2.43%) each. It should be noted that the CVC contamination level we determined in our study is below the average in Russia.

Thus, according to the data of B.V. Berezhanskiy (2006), it was revealed that CVC contamination takes place in more than 16% of cases. The obtained data reflect the importance of selecting an antibacterial drug on the basis of local microbial data on the range of causative agents and their resistance in the particular department. Anti-infectious therapy should be prescribed within 1 hour of sepsis identification. Initial empirical therapy should include 1 or more broad spectrum drugs, which are active against the most possible pathogens and capable of providing adequate concentration in the assumed infectious nidus. Antibacterial therapy (de-escalation) should be corrected after 48-72 hours, given the microbial study results [3].

Fungal CVC contamination and persistent hyperthermia with positive inoculations of blood cultures indicate the CVC removal. CVC-related infection should be monitored regularly; prompt action must be taken in case of even the slightest suspicion.

#### ***Central venous catheter's occlusion.***

CVC occlusion may be caused by the obstruction of catheter (thrombosis, PF solution's precipitation) or vein (thromboses or fibrin films). Moreover, occlusion may result from the causes, which are external in respect of CVC (catheter's tip is set against the venous wall, patient's position change leading to the compression of the CVC between a collar bone and rib I, known as the pinch-off syndrome).

Precipitation may be prevented by washing of the CVC with the 0.9% sodium chloride solution after each drug introduction or blood sampling. In case the CVC is not used, it should be washed with heparin solution. Use of line filters reduces the risk of ingress of admixtures into the CVC. Blood sampling from the CVC increases the risk of thrombosis due to the precipitation of fibrin threads; if possible, this procedure should be avoided or minimized; it must be planned thoroughly.

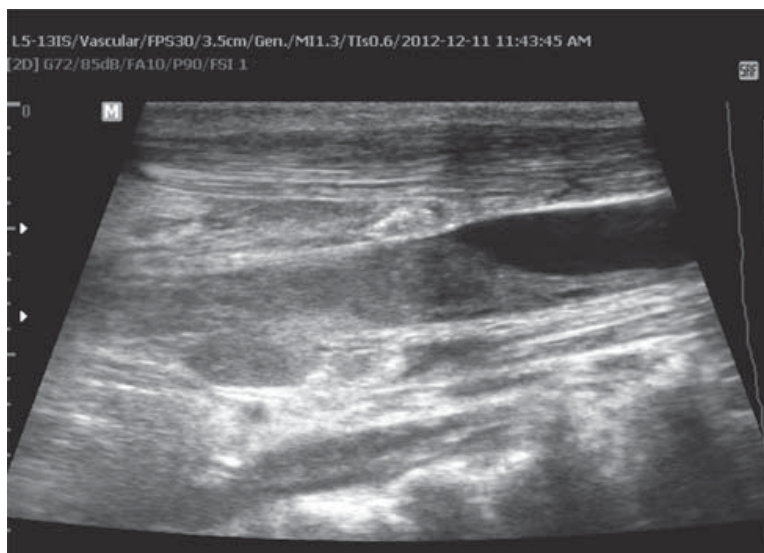
The pinch-off syndrome is characterized by local pain syndrome, which increases on movement, unsteady blood flow from catheter and high infusion pressure, which changes with the change in the patient's position.

In case of CVC thrombosis on early stages (after the first unsuccessful attempt at CVC blood sampling), catheter's thrombolysis with urokinase must be conducted. It is not recommended to use a line to restore CVC patency.

***Central venous thrombosis and pulmonary embolism.***

Central venous thrombosis and pulmonary embolism are potentially fetal complications. The risk of central venous thrombosis considerably increases if long-term PF is conducted for several weeks. Clinical symptoms of the central venous thrombosis in precava basin (the most often used venous access) are characterized by edematous face, collateral venous network's hypertension and/or pains on intravenous injections. Diagnostics of central venous thrombosis is based on echocardiographic and Doppler studies, computed tomography and/or angiography.

Pic. 1 gives a Doppler presentation of the right subclavian venous thrombosis



**Pic. 1.** Doppler presentation of the right subclavian venous thrombosis

Pulmonary embolism is characterized by chest pain, dyspnea, hemoptysis, syncope, tachypnea, tachycardia, hyperhidrosis and fever. "Minor thrombosis" may be asymptomatic or have indistinct symptoms, such as lassitude.

Central venous thrombosis and pulmonary embolism may be connected with relapsing CVC-infections, which are recurrent and associated with changes in the CVC position, proximal position of the CVC tip in precava or internal jugular vein, frequent blood sampling, introduction of concentrated glucose solutions or chemotherapeutic actions. Moreover, these complications may be idiopathic. The personnel should track non-motivated changes in children's condition (weakness, dyspnea, reddening or edemas around neck and limbs), CVC crippling and

dislocation, increase in pressure of infusion pumps. If these symptoms are revealed, it is necessary to appraise the situation promptly and take adequate action.

Acute symptomatic thrombosis is best treated using thrombolytic agents, however, the use of coagulants remains the most widespread therapeutic approach. In case thrombolytic complications are detected, reasonability of catheter removal should be considered, especially if it is infected. Vitamin K antagonists or low-molecular heparins are capable of reducing risk of thrombosis; they may be prescribed to patients on long-term PF or with the increased risk of thromboembolism [2, 5].

#### ***Extravascular position or damage of catheter.***

Extravascular CVC position is caused both by accidental and deliberate traction, which is why the CVC should be effectively secured on body surface to prevent bends, damage and movement of catheter in the tunnel. Aseptic adhesive bandage is routinely replaced (at least once in 7 days), in case of catheter's seal failure (wet bandage, bleeding), development of perifocal edema or dirty bandage.

Operability of long-term CVCs (including implantable CVCs) is restricted; a catheter may cripple with time – fractures, ruptures or loose connections may appear. In case such complications are revealed, it is necessary to replace the damaged element or reinstall the CVC. Bleeding is a life-threatening condition in case the catheter is damaged or the connection is insecure. In order to reduce the rate of this complication, it is reasonable to use infusion systems equipped with the “Luer lock” system.

#### **Compatibility**

Stability means that the mixture or solution preserves its physicochemical properties after a certain period of time:

- stable size of lipidic particles;
- no precipitation of insoluble complexes forming from the mixture components;
- availability of all components;
- no chemical reactions between components.

According to the recommendations of manufacturers, introduction of mono-component drugs or of “two-in-one” or “three-in-one” PF drugs is permissible. In the former case, separate introduction of carbohydrates with electrolytes, amino acids and lipids takes place. “Two-in-one” mixture contains amino acids, carbohydrates and electrolytes in container 1 and lipid emulsion in

container 2. “Three-in-one” mixture contains all the listed components, including lipids, in a single container.

“All-in-one” mixtures are parenteral feeding solutions containing water, glucose, 15-20 amino acids, lipids, 10-12 electrolytes, 9 microelements and 11-12 vitamins in a single container. Up to 100 chemical substances, that the mixture contains, have a huge interaction potential.

“Three-in-one” mixtures are introduced using one line; the manufacturer confirms the stability of emulsion parameters. Research of compatibility of “two-in-one” components, conducted by manufacturers, does not usually guarantee lipid emulsion’s stability in the final solution. Lipid emulsion is infused “separately”, although in practice it usually means infusion using the same infusion line through the Y-shaped set, which does not guarantee stability of the introduced components, which is why it is recommended to use terminal filters when conducting PF (pic. 2) [6].



**Pic. 2.** Infusion filter (1.2mcm) for fat emulsions

“All-in-one” system’s stability includes several complicated processes of chemical and physical interactions, which is why it is not safe to mix all components in the amounts prescribed by drugs; thus, it is recommended to prepare “all-in-one” mixtures in conformity with the checked indications of types and amounts of macro- and micronutrients in the strictly controlled conditions. It is necessary to conduct visual aggregation check of the mixture, emulsion separation and disintegration of the emulsion prior to and in the process of introduction.

### **Drug interactions**

There are 3 main types of interaction of PF and drugs:

- standard physiological interaction, which occurs always;
- alteration of physicochemical properties of drugs in the setting of unbalanced PF with dysmetabolic disorders;
- direct chemical interaction in syringe during introduction of drugs.

Hyperglycemia caused by diabetogenic action of glucocorticosteroids or hypoglycemia accompanying insulin introduction is an example of pharmacological effects of the first type.

These are predictable effects of the introduced drugs. In the second variants, altered acid-base balance and low plasma albumin level may result in the alteration of drug-receptor interactions and disturbed binding of metabolites with proteins. E.g., it is difficult to dispose of metabolic acidosis using sodium bicarbonate in a patient with high non-metabolizable base level, which takes place, e.g., at hyperchloremic metabolic acidosis. In the same way, we may note reduction in loop diuretics' efficacy in patients with hyponatremia.

There are many works reflecting physical and/or chemical stability of various drugs in particular PF mixtures. It is rather difficult to interpret these data, as drugs often contain excipients and adjuvants, which are necessary to produce drugs, apart from the active substance. That is why the present data are to be seen as specific to a particular proprietary product. E.g., pH of the PF mixture is usually similar to pH of the mixture of amino acids it contains; however, different drugs, which are present in the market, have pH from 5.0 to 7.0. The drug, which significantly dissociates at pH=5.0, may completely decompose at pH=7.0. That is why it is impossible to extrapolate results of studies of how different mixtures affect each other [2].

This problem appears to be even more complicated due to the behavior of fluids in infusion lines, especially if the flow speed is low. Sharp angles and hanging loops may form spaces with non-circulating fluid within systems, where drugs may stagnate; this may result in precipitation of drugs, "separation" of fat emulsions and alteration of the components' physicochemical properties. That is why it is extremely important to observe manufacturers' recommendations on the use of particular PF formulae. Moreover, the use of terminal filters and multichannel CVC reduces the risk of metabolic disorders at PF (pic. 3).



**Pic. 3.** Three-channel venous catheter

### **“Refeeding” syndrome**

The “refeeding” syndrome was first described during the Second World War, when sudden deaths were noted among prisoners-of-war and concentration camp inmates in case of nourishing date after long-term starvation. Autopsy did not reveal a visible cause of fatal outcome, excluding significant size reduction of internal organs (heart, liver, spleen etc.). Later, in 1977, J.P. Knochel suggested a hypothesis that death in these people was caused by hypokalemia and

hypophosphatemia. Patients in critical may also experience significant reduction in potassium, phosphorus and magnesium blood serum content soon after enteral or parenteral nutritive support has begun [7].

Malnutrition is a fairly widespread phenomenon. A meta-analysis, which combined 18 European and North American medical centers, appraised nutritive status of 10,000 inpatients. Malnutrition syndrome was revealed in 31% of cases [8]. Recommendation on PF in the initial phase are given below [2].

*Water and sodium overload may be prevented by:*

- limiting water and sodium consumption (down to 60% of physiological need in some cases) depending on degree of hydration;
- body weight monitoring: it is desirable to maintain stable body weight or even reduce it in the first 2-3 PF days;
- controlling and maintaining oncotic pressure by introducing albumin at 1g/kg;
- current water loss monitoring (perspiration loss, loss through gastrointestinal tract and fluid sequestration in intestines, abdominal and pleural cavities).

In clinical practice, body weight, diuresis, electrolytic blood and urine composition changes must be registered at least once a day on the early PF stage.

***Prescription of carbohydrates.***

Steady glycemia level maintenance requires, on the one hand, thorough glycemic profile monitoring, on the other – continuous glucose introductions due to the limited carbohydrate pool. That is why steady glucose infusion speed is set when conducting initial PF; this speed cannot be lower than the body glucose synthesis speed. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the following calculation of the initial glucose introduction speed for children of different age groups [2]:

- premature children – 4-8mg/kg per minute, increase by 1-2mg/kg per minute per day;
- term infants and children under 2 years of age – 7-8mg/kg per minute, increase by 2-4mg/kg per minute per day;
- children over 2 years of age usually require 6-9mg/kg per minute;
- children in critical state – not more than 5mg/kg per minute (7.2g/kg per day).

***Hypokalemia correction.***

Hypokalemia must be corrected regularly, taking into consideration renal and cardiac functions. Patients with malnutrition feature reduction in the ability to introduce potassium in metabolic processes, which is caused by low energy facilities, deficiency in proteins and their synthesis.

That is why an extremely fast hypokalemia correction should be avoided on the early PF stage, as it may be accompanied by hyperkalemia and heart rate disorders

#### ***Hypophosphatemia correction.***

According to the ESPEN recommendations, hypophosphatemia should be corrected gradually, taking into consideration neurologic status and renal functions. The initial phosphate dose is 0.5mmol/kg with gradual dose increase up to 1.0mmol/kg per day in proportion to protein load. Unfortunately, there are no commercial phosphorus-containing PF drugs in the Russian market. Thorough phosphatemia and phosphaturia monitoring is obligatory; it is aimed at phosphaturia restriction.

#### ***Proteins and energy needs.***

Fast correction of protein catabolism is impossible in the initial PF period, which is why the energy arrear should be corrected slowly, taking into consideration low baseline metabolic level and the preceding malnutrition [9]. Excessive nitrogen (crystal amino acid) prescription may result in hyperammonemia and/or metabolic acidosis in case renal clearance capacity for hydrogen and phosphate is exceeded. Parenteral prescription of amino acids at 0.5-1g/kg per day is enough to maintain the normal amount of blood plasma amino acids. When correcting protein malnutrition, it is important to provide simultaneous supply of both nitrogen and calories in right proportion.

#### ***Balance of nutrients.***

Right proportion of macro-elements, electrolytes, vitamins and micro-elements should be observed at PF. Disproportions may usually be prevented by introducing nutrients in the following proportions: 200-250kcal per 1g of nitrogen, 1.8mmol of calcium, 2.9mmol of phosphorus, 1.0mmol of magnesium, 10mmol of potassium, 7mmol of sodium and chlorides and 1.2mg of zinc.

#### ***Monitoring.***

The following parameters should be monitored at PF: rates of infusion, body temperature, cardiac and respiratory functions, diuresis, stool and body weights. Osmolality, glucose and protein content and pH should be controlled within the first 5 days and in case osmotic stress is increased. Parameters of blood plasma and urine electrolytes, calcium, phosphorus, magnesium, glucose and hematocrit must be registered twice within the first week, then – once a week. Proteinogram and parameters of albumin, bilirubin, alkaline phosphatase and aminotransferases should be evaluated regularly.

#### **Metabolic bone diseases**

Metabolic bone diseases in adults as a complication of long-term PF are characterized by the bone mineral density reduction, osteoporosis and pathological fractures. There are few works on

the development of such complications in children [10]. Bone mineral density reduction is a multifactorial state caused both by the primary disease and the PF-associated causes: excess of vitamin D, phosphorus, nitrogen and amino acids, calcium metabolic disorder, energy imbalance and aluminum contamination of solutions. Level of general calcium serum concentrations, free (ionized) calcium, phosphates, parathyroid hormone and vitamin D and alkaline phosphatase (bone fraction) activity must be regularly controlled and bone mineral density must be regularly evaluated in children receiving PF.

### **Hepatobiliary complications**

Children requiring long-term PF belong to the group of high risk in terms of development of renal diseases, most of which have transitory character and are reversible after PF has been cancelled. Long-term PF results in severer consequences: cholestasis, cholelithiasis, fibrosis and steatosis. Pathogenesis of liver damage at PF remains not completely clear [11]. It is likely to be a multifactor interaction caused by the primary disease, infection and PF components.

Hepatic malfunctions are registered on the 7<sup>th</sup>-14<sup>th</sup> PF day in the form of increase in level of transaminases and bilirubin; however, histologic study of hepatic tissue does not confirm pathological alterations. The listed deviations are transitory and do not depend on the presence of fat emulsions; in most cases, parameters normalize after PF has been stopped.

Histologic alterations appear in Kupffer cells in the form of grumous saccules in case of a long-term intravenous introduction of fat emulsions (for more than 1 month). The role of such fat depositing is not completely clear yet.

Cholestatic jaundice as a complication of complete PF is more often observed in infants; apparently, it is connected with immaturity of biliary system's excretory function. 2-3 weeks after PF has been stopped cholestatic jaundice disappears; however, in complicated cases it may progress up to the severe hepatic failure. Enteral feeding exclusion and short bowel syndrome cause lack of bile flow stimulation and recirculation of bile acids. It is likely that they take the leading role in pathophysiology of cholestasis development and hepatic failure progression.

Ileus, intestinal motility disorder and ileocecal valve's resection lead to the ascending colonization of small intestine with colonic flora. Intestinal mucous tunic's dystrophy is accompanied by intestinal microflora translocation to portal blood flow and destructive action of lipopolysaccharide of gram-negative flora on hepatobiliary system. All these factors favor the development of cholestasis as a PF complication [12].

It is extremely important monitor hepatic functions during PF. Early and the most sensitive markers of hepatic dysfunction are alkaline phosphatase and gamma- glutamyltransferase, while significant increase in bilirubin concentration may develop in the setting of cholestasis progression. Prevention and treatment of cholestasis:

- enteral feeding with breast milk or substitutes containing long-chain triglycerides;
- use of metronidazole to weaken bacterial growth and translocate bacteria in case of entodermal canal passage disorder and/or making of ileostomy or enteroplasty;
- early use of cyclic PF;
- preventive prescription of ursodeoxycholic acid or taurochenodeoxycholic acid as hepatoprotectors; in case activity of aminotransferases, alkaline phosphatase or bilirubin concentration is increasing – ursodeoxycholic acid therapy;
- timely decision of possibility of liver transplantation to children with unfavorable prognosis; unfavorable prognosis criteria: more than 3-months-long PF, bilirubin level higher than 50mcmol/l, number of platelets less than  $100 \times 10^9/l$ , prothrombin time of more than 15 seconds, partial thromboplastin time of more than 40 seconds and hepatic fibrosis [2].

Balanced parenteral feeding allows adequate provision of a child's body with amino acids, carbohydrates, fats and energy necessary to maintain the baseline energy level and correct the preceding malnutrition. PF has gained a steady position in the complex therapy of children in critical state. Unfortunately, long-term PF cannot serve as an absolute replacement of enteral feeding and is associated with complications of varying severity: from transitory and mild to severe, which require operative intervention, liver transplantation, and up to fatal. Knowledge of modern recommendations will help the reader to successfully overcome problems associated with complete long-term PF.

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