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Analysis of critical chemotherapy complications in children with acute leukemia and ways of their corrections

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Providing intensive care for critical conditions in pediatric hematological malignancies has its features and remains one of the most urgent tasks of pediatrics.

Purpose — to assess the features of critical conditions in children with acute leukemia (AL) and to review the literature for their correction.

Materials and methods. An analysis of the results of clinical, laboratory, and instrumental examination of 70 children treated in the Intensive Care Unit with AL aged from 1 month to 18 years has been carried out. Statistical analyses of data were conducted by STATISTICA 8.

Results. Among the complications of cytostatic therapy, the following ones have been recorded: neutropenia (in 62 cases), agranulocytosis (16), hyperleukocytosis (1); critical thrombocytopenia (15) with the development of severe hemorrhagic syndrome (10) and hemorrhagic shock (2), disseminated intravascular coagulation syndrome (1); anemia of II–III degree (12), involvement of gastrointestinal tract in the form of stomatitis/esophagitis/gastroenterocolitis (16), hepatitis (21), pancreatitis (2), cardiopathy (2), cardiovascular failure (1), interstitional pneumonia (1), respiratory failure (6), acute renal failure (2), focal neurologic signs/seizures (2). Infectious complications included pneumonia (22), including one with acute lung destruction (5), pneumonia complicated by pleurisy (2) or pneumothorax (3), pyelonephritis (3), otitis media (3), contact peritonitis (2), meningitis (2), central vein phlebitis (4) with superior vena cava syndrome (2). The combination of pneumonia with other infectious foci was determined in 17 patients. Sepsis was diagnosed in 6 cases.

Conclusions. In the examined patients there was a significant proportion of complications on the background of chemotherapy treatment of AL. The timely diagnosis and adequate correction of the complications can potentially reduce the mortality of AL.

The research was conducted according to principles of Declaration of Helsinki. Protocol of research was proved by local ethical committee, mentioned in institution's work. An informed consent was collected in order to carry out the research.

No conflict of interests was declared by the authors.

Keywords: intensive care, complications, chemotherapy, acute leukemia, children, infections, sepsis.

Критичні ускладнення хіміотерапії в дітей з гострою лейкемією та шляхи їхньої корекції

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Надання інтенсивної терапії за критичних станів, які виникають на тлі злоякісних гематологічних захворювань у дітей, має певні особливості і залишається одним із найактуальніших завдань педіатрії.

Мета — надати клінічну характеристику критичних станів у дітей з гострою лейкемією (ГЛ); провести огляд літератури щодо шляхів їхньої корекції.

Матеріали та методи. Проаналізовано результати клініко-лабораторного та інструментального обстеження 70 дітей, які перебували на лікуванні у відділенні реанімації та інтенсивної терапії з ГЛ віком від 1 місяця до 18 років. Для статистичного аналізу використано програму «STATISTICA 8».

Результати. Серед ускладнень цитостатичної терапії зафіксовано: нейтропенію (у 62 випадках), агранулоцитоз (16), гіперлейкоцитоз (1), тромбоцитопенію, нижчу за критичну, (15) з розвитком вираженого геморагічного синдрому (10) та геморагічного синдрому, шок (2), синдром дисемінованого внутрішньосудинного згортання (1), анемію II–III ступеня (12), ураження шлунково-кишкового тракту у вигляді стоматиту/езофагіту/гастроентероколіту (16), гепатит (21), панкреатит (2), кардіопатію (2), серцево-судинну недостатність (1), інтерстиціальну пневмонію (1), дихальну недостатність (6), гостру ниркову недостатність (2), вогнищеві неврологічні симптоми/судомні напади (2). Серед інфекційних ускладнень — пневмонія (22), у тому числі з гострою деструкцією легень (5), пневмонія, ускладнена плевритом (2) або пневмотораксом (3), пієлонефрит (3), отит (3), контактний перитоніт (2), менінгіт (2), флебіт центральної вени (4) із синдромом верхньої порожнистої вени (2). У 17 хворих встановлено поєднання пневмонії з іншими інфекційними вогнищами. У 6 випадках діагностовано сепсис.

Висновки. В обстежених хворих виявлено значну частку ускладнень на тлі хіміотерапевтичного лікування ГЛ. Своєчасна діагностика та адекватна корекція ускладнень потенційно може знизити рівень смертності від ГЛ.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення дослідження отримано інформовану згоду батьків, дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: інтенсивна терапія, ускладнення, хіміотерапія, гостра лейкемія, діти, інфекції, сепсис.

Introduction

Despite the success in treatment and improvement of survival rates in childhood leukemia patients in recent decades, numerous complications of chemotherapy in children with acute leukemia (AL) worsen the course of the disease, reduce the effectiveness of treatment, and often determine an unfavorable prognosis of the disease [6]. Among the unfavorable complications, infectious complications are of leading importance [5,10,12], among them sepsis, infectious-toxic shock [1,7], and also hematological complications, including bleeding [11,20,22].

Up to date, there is a special term «treatment-related mortality», that is used to describe deaths connected with complications of therapy and drug toxicities. In addition, as infections are one of the main causes of fatal outcomes in pediatric leukemia patients, the special term «infection-related mortality» was introduced for deaths of infectious

origin. Any fatal outcome that occurs in the presence of a clinically documented or microbiologically confirmed infection is classified as «infection-related mortality» [16]. Therefore, timely diagnosis and adequate management of infections on the background of chemotherapy (CT) is one of the ways to reduce the mortality of children with AL.

The study of complications and critical conditions in children with AL and their proper treatment is a task of great importance in pediatric hematology that can improve the prognosis of the main disease [6,17].

The ***purpose*** of the study — to assess the features of critical conditions in children with acute leukemia (AL) and to review the literature for their correction.

Materials and methods of the research

An analysis of case histories of 70 children with AL aged from 1 month to 18 years was carried out. All these children were treated in the Intensive Care Unit (ICU) the Municipal Children's Clinical Hospital No. 16, Kharkiv.

The diagnosis and treatment of AL were established according to the diagnostic criteria specified in the orders of the Ministry of Health of Ukraine No. 364 dated 20.07.2005 «Pediatric Hematology», No. 617 dated 23.07.2010 «About changes to Ministry of Health of Ukraine order dated 20.07.2005 No. 364» On approval of protocols for providing medical care to children in the specialty «Pediatric hematology» [14,15], that are based on international protocols «Acute Lymphoblastic Leukemia Intensive Chemotherapy Berlin Frankfurt Munich 2009» (ALL IC BFM 2009) and «Acute myeloid leukemia-Berlin-Frankfurt-Munster (AML-BFM) 2004».

Statistical analyses of data were conducted by STATISTICA 8 (Tulsa, OK). Shapiro–Vilka test has been used for verification of the distribution according to the Gauss law. The samples had a non-normal distribution, so we used median (Me), and interquartile range (Lq — lower, quartile; Uq — upper quartile) for the statistical analysis. The difference in the parameters has been considered significant at $p<0.05$.

Results of the research and their discussion

The study involved 70 children with AL. The general characteristics of patients with AL and the main laboratory test in the ICU depart-

Table 1

General characteristics and laboratory tests of children with acute leukemia at the time of admission to ICU department (n=70)

Parameter	Units	Value
Age	Me (Uq; Lq) years	5 (2; 9)
Gender Male/Female	n %	47/23 67.1%/32.9%
Type of leukemia ALL/AML	n %	58/12 82.9%/17.1%
Risk group Standard/High	n %	53/17 75.7%/24.3%
Hemoglobin	Me (Uq; Lq) g/l	103.0 (90.0; 116.0)
Erythrocytes	Me (Uq; Lq) 10^{12}/l	3.3 (2.9; 3.8)
Leukocytes	Me (Uq; Lq) 10^9/l	1.3 (0.7; 2.4)
Platelets	Me (Uq; Lq) 10^9/l	115.0 (48.0; 153.0)
Erythrocyte sedimentation rate	Me (Uq; Lq) mm/hour	7.0 (4.0; 20.0)
Alanine aminotransferase (ALT)	Me (Uq; Lq) mmol/(l×hour)	1.0 (0.5; 1,4)
Creatinine	Me (Uq; Lq) μmol/l	66.5 (59.0; 80,0)
Urea	Me (Uq; Lq) mmol/l	3.6 (5.2; 3.8)
Uric acid	Me (Uq; Lq) mmol/l	0.26 (0.21; 0.29)
C-reactive protein (CRP)	IU/ml	7.2 (0.0; 13.2)
Total protein	Me (Uq; Lq) g/L	58.0 (51.8; 62.7)
Albumins	Me (Uq; Lq) %	56.8 (54.0; 64.0)
Globulins α1 α2 β γ	Me (Uq; Lq) %	 4.5 (2.9; 5.5) 10.0 (7.8; 11.4) 10.8 (8.8; 12.8) 19.0 (13.8; 21.5)
Ionized calcium	Me (Uq; Lq) mmol/l	0.84 (0.73; 0.98)
Sodium	Me (Uq; Lq) mmol/l	135.80 (134.80; 139.30)
Potassium	Me (Uq; Lq) mmol/l	3.40 (3.19; 3.58)
pH of blood	Me (Uq; Lq) units	7.40 (7.37; 7.45)

ment are presented in Table 1. There was a significant (p=0.002) prevalence of boys than girls. Among the morphological variants of leukemia, lymphoblastic leukemia was most likely (p<0.001).

As it is evident from Table 2, changes in complete blood count were typical for children with AL, such as neutropenia, anemia and thrombocytopenia. It proves the suppressive effect of CT on bone marrow. There was a high level of ALT as a result of toxic effect on liver. Increased CRP is marker of active inflammatory process.

For the next step we assessed he complications of cytostatic therapy in AL children treated in ICU department, which are presented in Table 2.

Hematological complications, on the background of CT were the most frequent and presented in 63 (90.0%) children. Neutropenia was presented in the majority of children (62 (88.6%) cases), including agranulocytosis (16 (22.9%) cases). As a result of high frequency of neutropenia infection complications were common in patient with AL (60.0%). Complications of CT with the development of nosocomial infection were found in 42 (60.0%) patients with AL. Infectious complications included pneumonia (22 (31.4%) cases), stomatitis/esophagitis/gastroenterocolitis (16 (22.9%) cases), pyelonephritis (3 (4.3%) cases), otitis media (3 (4.3%) cases), contact peritonitis (2 (2.8%) cases), meningitis (2 (2.8%) cases), central vein phlebitis (4 (5.7%) cases) with superior vena cava syndrome (2 (2.8%) cases). Pneumonia had a tendency to be severe and in some cases was complicated with acute lung destruction (5 (7.1%) cases of all pneumonias), pneumonia complicated by pleurisy (2 (9.0%) cases), pneumothorax (3 (4.3%) cases) and respiratory failure (6 (8.6%) cases). The combination of pneumonia with other infectious foci was determined in 17 (24.3%) patients. Sepsis was diagnosed in 6 (8.6%) cases. The primary site of infection was not identified in 6 children. The systemic inflammatory response syndrome (SIRS) was explained by the translocation of the infection from the gastrointestinal tract.

Critical thrombocytopenia (below 70×10^9/l) was also common and reordered in 15 (21.4%)

Table 2

Frequency of AL complications at ICU department (n=70)

Complication		Total	
		n	%
Hematologic	Neutropenia	62	88.6
	Agranulocytosis	16	22.9
	Hyperleukocytosis	1	1.4
	Thrombocytopenia below the critical level	15	21.4
	Hemorrhagic syndrome (rash/bleeding)	10	14.3
	Hemorrhagic shock	2	2.8
	Disseminated intravascular coagulation syndrome	1	1.4
	Anemia of II–III degree	12	17.1
Complications of the gastrointestinal tract	Toxic hepatitis	21	30.0
	Stomatitis	16	22.9
	Esophagitis/gastroenterocolitis	15	21.4
	Pancreatitis	2	2.8
	Contact peritonitis	2	2.8
Complications of respiratory system	Interstitial pneumonia	1	1.4
	Pneumonia	22	31.4
	Acute lung destruction	5	7.1
	Pleurisy	2	2.8
	Pneumothorax	3	4.3
	Respiratory failure	6	8.6
Complications of urinary tract	Pyelonephritis	3	4.3
	Acute renal failure	2	2.8
Complications of the cardiovascular system	Cardiomyopathy	2	2.8
	Cardiovascular failure	1	1.4
	Central vein phlebitis	4	5.7
	Superior vena cava syndrome	2	2.8
Complications of the nervous system	Focal neurologic signs / seizures	2	2.8
	Meningitis	2	2.8
Other	Sepsis	6	8.6

Table 3

Spectrum of microorganisms in different biological media in children with infectious complications of acute leukemia chemotherapy

Microflora	Total	Sputum	Urine	Blood	Other
Str. Pneumonia	24	22			2
Str. Faecalis	8	3		1	4
Str. Mitis	3	3			
Str. Epidermitidis	10	2	4	2	2
St. Aurheus	14	7		3	4
Klebsiella Pneumonia	5		3	2	
E. Coli	6	1	4		1
Ps. Aeruginosa	21	10	8	3	
Proteus mirabilis. & vulgaris.	5	1	2	1	1
Total	**96**	**49**	**21**	**12**	**14**

cases. As a result, hemorrhagic complications developed in 10 (14.3%) cases, that in some cases were complicated by hemorrhagic shock (2% (2.8%) cases), disseminated intravascular coagulation syndrome (1 (1.4%) cases). Anemia of II–III degree was presented in 12 (17.1%) cases.

Toxic effects of CT were also registered in 22 (31.4%) cases, mainly toxic hepatitis (21 (30.0%) cases). In addition, there was 1 (1.4%) case of interstitial pneumonia, that was probably induced by CT toxicity and developed during HR-protocol.

Neurological signs in form of focal neurologic signs/seizures in 2 (2.8%) children were connected with such critical condition as neuroleukemia.

The relation between the initial severity of the patient's condition, the number of CT complications, and infectious complications were revealed. Most patients had a combination of different complications. In patients with AL at the stage of treatment in the ICU, 65% had 3–4 complications, and 35% had 5 or more. In some cases, critical insufficiency of system of organs developed, such as respiratory failure (6 (8.6%) cases), cardiovascular failure (1 (1.4%) case), acute renal failure (2 (2.8%) cases).

Microbiological tests of blood, urine, and cerebrospinal fluid, conducted before the start of CT, gave a negative result, no pathogenic microflora was cultured in feces, streptococci (7) and staphylococci (2) were cultured in the throat of 9 patients. When complications develop (more often at 2–3 weeks of therapy), microbiological studies have shown significant colonization. 96 positive results of bacteriological studies were obtained, which averaged 2.2 per patient. The frequency of detected various strains of microorganisms in blood, urine, sputum, and other media is presented in table 3.

The leading place in the frequency of nosocomial infection was occupied by strepto-staphylococcal flora. Among gram-negative bacteria *Pseudomonas aeruginosa* dominated. Resistance to all antibiotics *in vitro* was found in 3 strains of staphylococcus and 3 strains of *Ps. Aeruginosa*.

It is important to note, that timely and adequate correction of critical complications of AL can improve survival rate of this patients [6,17]. Therefore, we analyzed the potential ways of their correction by literature review.

Up to date therapy of septic complications should include two mandatory components, such as the elimination of the causative agent and immunity disorders [10,12,13]. The modern arsenal of antibiotics ensures reliable suppression of pathogens, if antibiotic therapy is timely, as the «golden hour rule» recommend. When the pathogen is detected, it is targeted [1,5]. Early antibiotic therapy is prescribed based on the localization of the primary focus of infection and its prevalence, the algorithm for the use of which is presented in Fig. 1.

In recent years, the microbial flora and the sensitivity of microorganisms to antibiotics have changed, so changes have been made to the drug-prescribing algorithm. Thus, in the 2nd phase, in the development of infectious-toxic shock (ITS), carbapenems, fluoroquinolones and antimycotics, or cephalosporins of the IV generation and aminoglycosides were used in combination with immunoglobulin intravenously at a dose of 400 mg/kg/day within 5 days, or 1000 mg/kg/day within 2 days. Such an empirical prescription (escalation) of antibiotics to maximally block the entire range of possible infectious agents in combination with immunotherapy has shown high effectiveness in sepsis and ITS in most patients. When identifying the causative agent (targeted antibiotic therapy), it is rational to use the following tactics [18,19,23]. If a staphylococcal pathogen is assumed, its possible resistance to methicillin

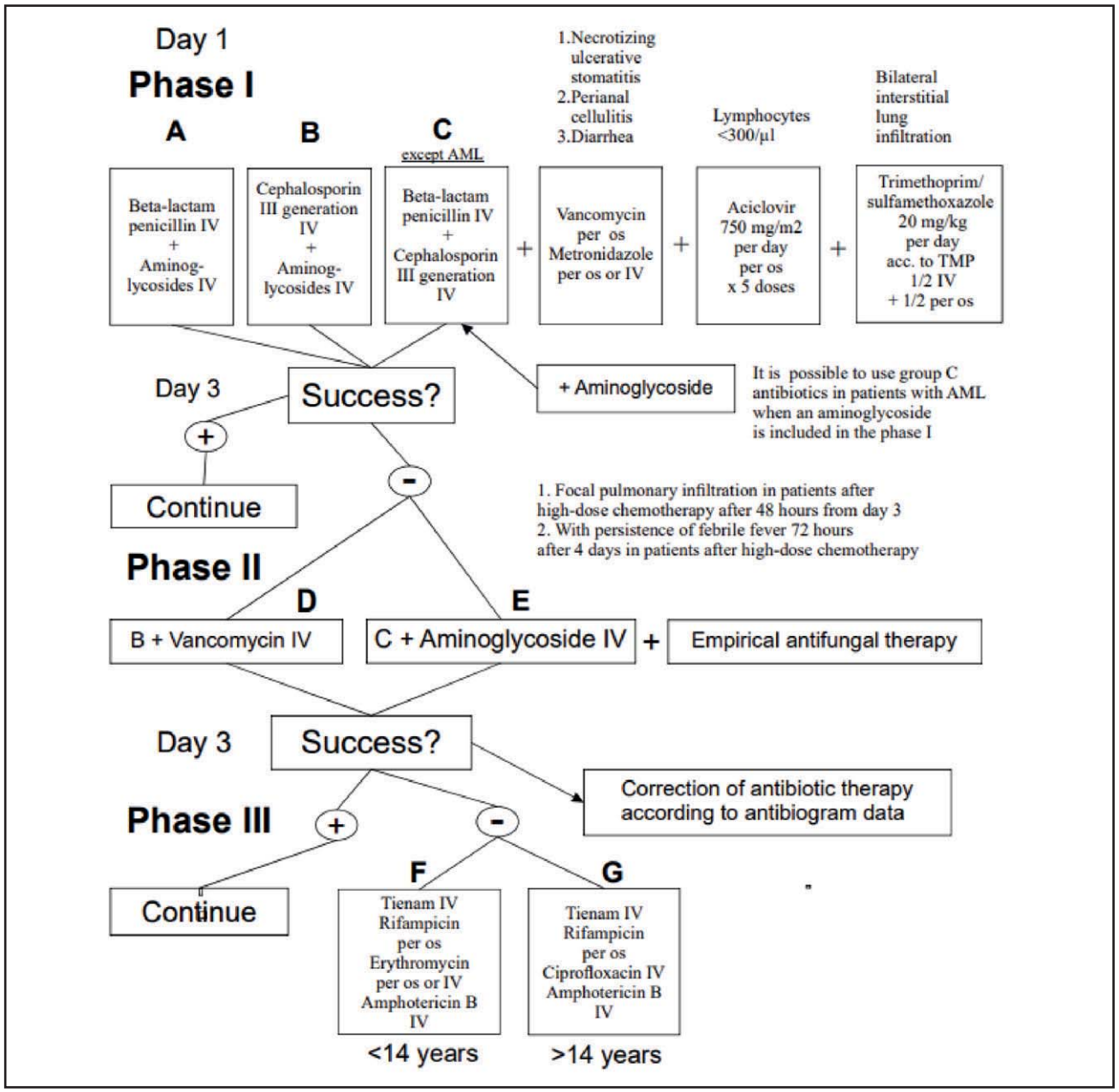

Fig. 1. Algorithm for prescribing antibiotics for complications of chemotherapy in patients with acute leukemia

should be considered. It is advisable to start with beta-lactam semi-synthetic penicillins or anzamycins, it is possible to use III-generation cephalosporins or lincosamides in combination with aminoglycosides or fluoroquinolones. IV-generation cephalosporins, glycopeptides, or linezolid should be reserved for gram-positive sepsis. If gram-negative sepsis is suspected, it is advisable to prescribe carboxypenicillins, including beta-lactams, as well as monobactams. It is possible to use III-generation cephalosporins or fluoroquinolones in combination with aminoglycosides. As a reserve for gram-negative sepsis, there are cephalosporins of the III–IV generations and carbapenems.

In cases of suspected fungal or fungus-associated etiology of sepsis, we prefer Amphotericin B (fungizone, fluconazole) and Diflucan. Drugs of choice in the treatment of invasive aspergillosis are itraconazole and voriconazole [3].

The timing of antibiotic discontinuation in the successful treatment of sepsis is determined empirically. Five days of normal temperature in the presence of signs of sanitation of the septic site is an approximate term for their cancellation. Discontinuation of antibiotics too early may lead to the recurrence of sepsis.

Roncoleukin is recombinant interleukin-2 (IL-2) that turned out to be the most promising

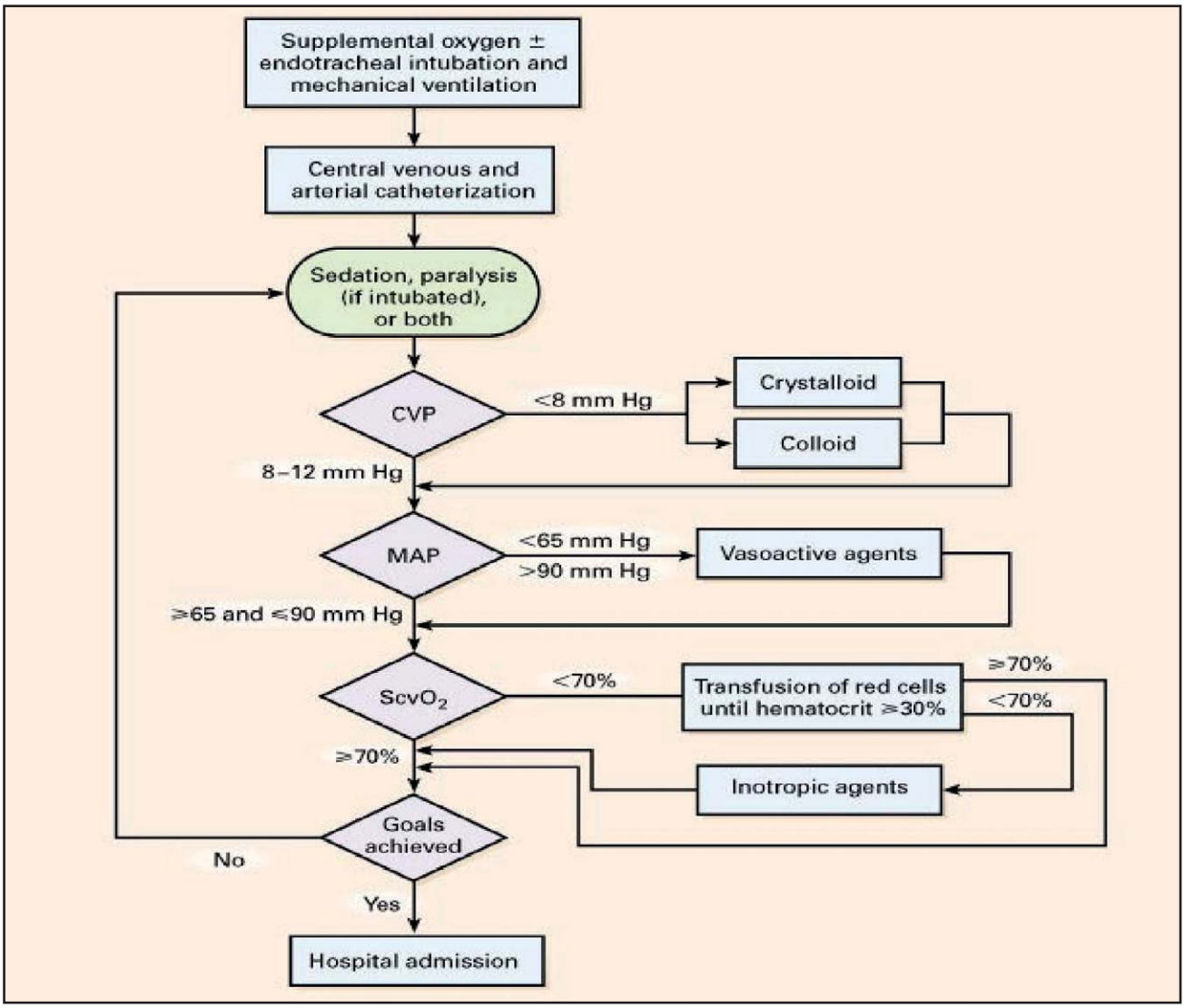

Fig. 2. Protocol for Early Goal-Directed Therapy [21], where CVP is central venous pressure, MAP is mean arterial pressure, and $ScvO_2$ is central venous oxygen saturation

drug for immune regenerative therapy of sepsis [24]. An additional means of immune corrective therapy of sepsis in the presence of leukopenia is the use of preparations of macrophage and granulocyte-macrophage colony-stimulating factors [2].

With the development of thrombocytopenia and hemorrhagic complications, we use platelet concentrate as a substitute [11,22]. Clinical observations indicate a direct dependence of the severity and frequency of the development of infectious and non-infectious complications in patients with myeloid depression on the duration of thrombocytopenia. The loss of the capillarotrophic function of platelets, which is accompanied by a violation of vascular wall trophic and the development of hemorrhages, is important. For preventive treatment of capillarotrophic disorders and hemorrhagic complications it is necessary to use of high-dose donor platelet concentrate in patients with AL with myelosuppression after CT [11]. Thus, following the protocol of leukemia treatment [14,15], the level of blood platelets in patients with AML was maintained at no lower than 70×10^9/l. In patients with ALL, when the level of blood platelets drops to 20×10^9/l and below, even in the absence of hemorrhagic manifestations, thromboconcentrate should be used. A comparison of the results of treatment of patients with AL who did not receive platelet concentrate and received adequate replacement therapy showed that the number of complications and the severity of their manifestations are significantly lower in the latter. The frequency of such complications as ITS, and bleeding decreased by 4 times, and severe pneumonia, and lesions of the gastrointestinal tract decreased by 2 times.

However, the transfusion of donor blood products, in addition to alloimmunization, is associated with the risk of transfusion reactions, the trans-

mission of hepatitis viruses, and human immunodeficiency virus. Therefore, the development of alternative approaches to prevent thrombocytopenia is needed. A promising direction of therapy is the stimulation of the platelet lineage of hematopoiesis by thrombopoietins. The use of recombinant IL-11 (Oprelvekin) in patients with AL with myelosuppression is accompanied by a dose-dependent increase in the number of megakaryocytes in the bone marrow and platelets in the blood, as well as a decrease in the severity and duration of thrombocytopenia [9]. However, the appointment of IL-11 can be accompanied by anemia, edema and cardiovascular system dysfunction, which limits its use in critically ill patients [8].

Therapy of shock in the acute phase is based on the implementation of successive stages, the task of which is to achieve the target (normative) values of the main parameters of hemodynamics. This is the so-called early meta-oriented therapy of severe sepsis and shock previously described by the authors E. Rivers, D. Nguyen et al. [21] and it is presented in the Fig. 2.

According to the early meta-oriented therapy of shock, in the acute phase, a number of measures (items) are performed sequentially, including:

1) Oxygen therapy with spontaneous breathing or artificial ventilation of the lungs (AVL).

2) Provision of reliable central venous access (or accesses) and arterial catheterization.

3) Sedation of patients or relaxation during ventilation.

4) Hemodynamic support includes provision of central venous pressure (CVP) within 80–120 cm Hg. (the norm for older children and adults) for which active rehydration is carried out by the introduction of colloidal and crystalloid solutions; the initial rate of infusion is 40–60 ml/kg of body weight in the first hour. The average CVP norm in children under 10 years of age is calculated using the formula: CVP = 25+5 (n — 1) cm of height, where n is the child's age in years.

5) If the goal is achieved, the next target indicator — mean arterial pressure (MAP) should be maintained within 65–90 mm Hg, for which vasoactive agents are used. At high MAP venous and arterial dilators are used, at low MAP the use of vasopressors is recommended. Vasodilators such as Benzohexonium in a dose of 0.5–1 mg/kg (single dose), Sodium Nitroprusside or its analogues in the form of continuous infusion is provided. Dose selection is individual according to the effect. Vasopressors such as Norepinephrine in a starting dose of 0.05–0.1 mg/kg or Dopamine in a dose of 12 and more μg/kg/min are inducted.

6) If the goal is achieved, the next target parameter is blood oxygen saturation in the central vein ($ScvO_2$), which should be at least 70%. This parameter is achieved in two ways: a) transfusion of donor erythrocytes if the hematocrit is less than 30% or hemoglobin is less than 90–100 g/l; b) using inotropic support by Dobutamine at a dose of 5–12 μg/kg/min or dopamine at a dose of 5–8 μg/kg/min. intravenously with systolic dysfunction of the myocardium of the ventricles. In the absence of the proper effect, it is possible to use phosphodiesterase inhibitors — Amrinone, Milrinone.

7) Further, the therapy of the main disease is continued, but if the goal is not achieved, it is necessary to return to point 3, conduct an analysis of the situation, exclude iatrogenic complications, correct the acid-base balance, electrolyte balance, warm the patient, continue measures to achieve the target values of CVP, MAP indicators, $ScvO_2$.

Conclusions

According to our study there was a significant level of critical complications in children with AL on the background of CT. The most common of them were hematological complications (90%), infections complications (60%), including sepsis (8.6%), hemorrhagic syndrome (14.3%), toxic hepatitis (30%). Most patients had a combination of different complications. 65% had 3–4 complications, and 35% had 5 or more. In most severe cases, critical insufficiency of system of organs developed, such as respiratory failure (8.6%), cardiovascular failure (1.4%), acute renal failure (2.8%).

The introduction of supportive therapy for the prevention of CT complications and adequate intensive care at the development of life-threatening complications can improve the prognosis of patients with AL.

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