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Use of blood and its components in the treatment of anaemia in children

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ABSTRACT

Blood transfusion is a well-established treatment for anaemia. Herein, blood and its components are transfused to replenish circulating blood volume, maintain the oxygen capacity of the blood and normalise the function of the coagulation system. Anaemia treatment by blood transfusions is a great challenge, especially with reference to paediatric patients. Blood is irreplaceable in a life-threatening situation, but it has its own side effects, just like all applied pharmacological products. Hence, it is extremely important to carefully select donors and utilise blood components according to the patient's individual needs. Children represent a group that requires specific criteria to be met, mainly because of the fact that their physiological and haematological systems differ from those of adults. The most common types of anaemia seen in children are deficiency anaemias such as iron-deficiency anaemia, while less common are vitamin B12 deficiency anaemia or folate deficiency anaemia. Secondary anaemia is also relatively frequent in chronic diseases, among others, immunological or infectious, as well as renal, liver, endocrine and neoplastic diseases. Anaemia due to blood loss is also included in this group. Furthermore, some anaemias, such as aplastic anaemia (due to impaired erythrocyte production) and haemolytic anaemia (due to excessive destruction of red blood cells) may be congenital or acquired. Before deciding to implement blood therapy, the patient's clinical condition or the different haematological, biochemical and immunological parameters at different stages of life should be considered. Since each transfusion may result in a variety of post-transfusion reactions, immunisation or transmission of infectious diseases, the decision to transfuse blood or blood components should be taken only when the patient cannot be treated effectively by any other means and the expected benefits of the transfusion outweigh the risks associated with possible complications. Considering the recipients' low blood volume, low metabolic efficiency, higher haematocrit levels than in adults and immature immune system, products for these patients should be prepared in a special way. These components must ensure minimal risk of metabolic and haemostatic disorders. The collection of these products, as well as their preparation, storage and transfusion, should be carried out in accordance with current legislation.

INTRODUCTION

Anaemia treatment by blood transfusions is a significant challenge, particularly in pae-diatric patients. Before deciding to implement blood transfusion, the patient's clinical condition or different haematological, biochemical and immunological parameters at different stages of life should be considered. It is, however, difficult to determine guidelines for blood transfusion in children.

AIM

This article reviews the literature on diagnostic assessment and treatment of anaemia in paediatric patients.

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MATERIALS AND METHODS

A review of available scientific articles was conducted using PubMed/MEDLINE, Web of Science and Google Scholar databases with a time range of January 1985 to March 2022. The search was conducted using the following keywords: 'anaemia', 'anaemia in children', 'anaemia treatment', 'transfusion', 'blood and blood components', 'post-transfusion complications', 'transfusion risks'. 69 opinions on transfusion merits or risks were selected from the articles found. Additionally, an overview of the most recent legislation on the use of blood and its components in healthcare was carried out.

RESULTS AND DISCUSSION

Classification of anaemia

Anaemia is a pathological condition in which haemoglobin (Hb) levels are below normal. The number of red blood cells and the amount of circulating haemoglobin are not sufficient for proper oxygenation of peripheral tissues, with numerous consequences [1-3]. Based on path-ogenetic mechanisms, anaemia can be divided into 3 main categories: (1) anaemia related to impaired erythrocyte production, (2) anaemia related to blood loss and (3) anaemia related to reduced erythrocyte lifespan [4-6]. Anaemia is also divided in terms of severity, the degree of which is determined by haemoglobin concentration. We can distinguish between grade 1 – mild anaemia (Hb: 9.5-10.9 g/dL), grade 2 – moderate anaemia (Hb: 8.0-9.5 g/dL), grade 3 – severe anaemia (Hb: 6.5-8.0 g/dL) and grade 4 – life-threatening anaemia (Hb <6.5 g/dL) [3].

Symptoms of anaemia include: weakness, irritability, loss of appetite, stunted growth, drowsiness, headaches and dizziness, visual disturbances, tinnitus, palpitations, pale or possibly yellowish skin, erosions at the corners of the mouth, oral mucositis, brittle hair and nails, and tachycardia (a functional systolic murmur over the top of the heart) [4,7-9]. In the case of anaemia in children, the symptoms are similar, but, interestingly, the causes vary according to age. In infants, these will include blood loss, alloimmunisation (ABO incompatibilities), con-genital infections (e.g. sepsis, B19 parvovirus, rubella), Diamond–Blackfan syndrome and Fanconi anaemia. In infancy and childhood, causes of anaemia include i.a. blood loss, iron deficiency, abnormal haemoglobin synthesis, glucose-6-phosphate dehydrogenase (G6PD) defect, leukaemia, and congenital haemolytic anaemias [10]. Anaemia, especially during the pre-school years, can cause abnormalities in behavioural and cognitive development. It also contributes to increased susceptibility to infection and mortality.

According to the World Health Organization (WHO), anaemia in children is diagnosed on the basis of haemoglobin concentration, taking into account the patient's age, i.e. with an Hb concentration <11g/dL for children aged 6 months to 6 years and with an Hb concentration <12 g/dL for children aged 6 to 14 years [11]. WHO estimated that the prevalence of anaemia in children aged 6 to 59 months worldwide in 2011 was 42.6%. Focusing on the European region, it was believed that 22.9% of all children aged 6 to 59 months had anaemia, which means 12.7 million anaemic children [12].

The most common form of anaemia in children is iron-deficiency anaemia. Vitamin B12 deficiency anaemia or folate deficiency anaemia are relatively rare. Iron deficiency anaemia is primarily observed between 6 and 24 months of age, but also in adolescents during puberty [5,13]. Deficiency anaemia is most often the result of a poorly balanced diet [14]. The risk of iron deficiency anaemia in newborns is increased by low birth weight, prematurity and multiple pregnancy [7]. Iron deficiency in the pregnant mother can also contribute to iron deficiency from early infancy [15]. Aplastic anaemia is associated with impaired erythrocyte production. This can be congenital or acquired. Congenital aplastic anaemia manifests itself at various times after birth, while acquired anaemia is usually seen in children over 6 years of age. It is relatively rare in children under 3 years of age [13,16]. Congenital bone marrow failure syndromes involving all marrow systems include Fanconi's aplastic anaemia. Failure involving one of the marrow systems is called Diamond–Blackfan anaemia (DBA). These are the most prevalent congenital bone marrow hypoplasias. They usually appear at birth or in the first weeks or months of life [17,18].

Secondary anaemia is the second most common type of anaemia worldwide, after iron deficiency anaemia, occurring in chronic diseases (immunological, infectious, renal, hepatic, endocrine or neoplastic) in which the decrease in haemoglobin and/or RBC count is directly related to pathological processes outside the haematopoietic system [19,20]. Anaemia due to blood loss belongs to the group of secondary anaemias. In neonates, it is mainly associated with blood loss during the perinatal period and subsequent developmental periods, but the main causes are trauma, GI diseases, urinary tract bleeding, recurrent nosebleeds and bleeding as-sociated with clotting disorders [19,13].

Haemolytic anaemia, caused by excessive destruction of red blood cells, can be congenital and acquired. The latter is much more common [13]. Congenital dyserythropoietic anaemia (CDA) belongs to the group of congenital anaemias. It is usually detected in the first decade of life, although in some patients, especially those with a mild form of the disease, the diagnosis is made in adulthood [19]. Congenital disorders also include anaemias associated with enzymatic disorders, so-called enzymopathies. G6PD and pyruvate kinase deficiency promote severe jaundice and anaemia in the neonatal period, and thereafter the course of the disease is usually asymptomatic, with periodic crises [7,18,19].

Among the congenital haemolytic anaemias we can also distinguish between anaemias associated with disorders of the erythrocyte membrane (e.g. spherocytosis) and haemoglobi-nopathies (e.g. thalassaemia). Spherocytosis is characterised by a deficiency or dysfunction of erythrocyte membrane proteins. This promotes a reduction in the osmotic resistance of the erythrocyte and increases sensitivity to damage [14]. The disease is usually diagnosed in childhood, often in infancy. Thalassaemia, on the other hand, belongs to the group of genetically determined haemolytic anaemias caused by disorders in the synthesis of globin chains. Thalassaemia is the most prevalent form of

anaemia in the Mediterranean, Africa and Asia. It is estimated that 4.83% of the world's general population carries a gene for one form of thalas-saemia. An increasing number of people are being diagnosed with this disease in Poland as well [5,8,19]. Among children, autoimmune haemolytic anaemia (AIHA) is rare, occurring mainly in pre-school age, although cases of the disease in infancy have been described. They are a group of diseases caused by the presence of autoantibodies to red blood cells [19]. Neonates may also develop haemolytic anaemia as a result of maternal-fetal serological conflict [8,21].

Diagnostic assessment of anaemia

Diagnostic assessment of anaemia should be based on medical history, physical exami-nation and laboratory diagnostics [2,7]. The basic parameter indicating anaemia is the haemo-globin (Hg) level. When interpreting haemoglobin levels, the patient's age and co-existing diseases should be considered. With anaemia, the parameters that should be proportionally reduced should be RBC (red blood cell count) and HTC (haematocrit). However, it should be noted that dehydration causes an increased HTC value, while a decreased HTC value is ob-served due to overhydration. [4,8,9,23]. At the same time, the size and shape of the RBCs, the level of reticulocytes and biochemical parameters that may indicate RBC breakdown should be analysed. WBC and platelet levels are also assessed to determine whether there is isolated anaemia or a multisystem disorder. If abnormalities in these systems are found, a morphological evaluation of the bone marrow cells should be performed [4,23].

Assessment of reticulocytosis provides considerable diagnostic information to determine whether the anaemia is due to impaired bone marrow function (reticulocytopenia) or excessive erythrocyte loss due to haemolysis or bleeding (reticulocytosis) [7]. Because the reticulocyte count is expressed as a percentage of total RBCs, it must be corrected according to the extent of anaemia by applying the following formula: reticulocyte % × (patient HCT/normal HCT) = corrected reticulocyte count. The most reliable result is that which is in absolute numbers, which should be 20-100 g/L in the non-anaemic state. If a RBC production disorder is suspected, a diagnostic bone marrow biopsy may be required [4,23].

Evaluation of peripheral blood smear allows for RBC evaluation – the presence of ba-sophilic granules may indicate thalassaemia, while Howell-Jolly bodies are observed in asplenia, pernicious anaemia and states of accelerated erythropoiesis. Moreover, Heinz bodies appear in thalassaemia, asplenia and chronic liver diseases, while Cabot rings can be observed in pernicious and haemolytic anaemia [7,19]. Of practical importance in differentiating anaemia is the division of anaemia according to the size of the red blood cell, which is also assessed during evaluation of the peripheral blood smear. The parameter that differentiates between microcytic, normocytic and macrocytic anaemia is the mean corpuscular volume (MCV). If the MCV is below 80 fL, microcytic anaemia can be suspected. MCV in the range of 80-100 fL refers to normocytic anaemia and MCV above 100 fL indicates macrocytic anaemia [5,6,23].

When interpreting this parameter in a child, the high variability of the parameter between developmental periods must always be reckoned with. Neonates and young infants have a physiologically higher MCV, which then decreases in the second quarter of life [19]. If mi-crocytic anaemia is suspected, a number of iron metabolism tests should be performed, among others, ferritin concentration, TfSat (transferrin saturation), TIBC (total iron-binding capacity – an approximate measure of transferrin concentration), free iron concentration, sTfR (soluble transferrin receptor in blood serum). In thalassaemia, a significant reduction in MCV (below 70 fL) with a disproportionately low reduction in RBC count is typical. Lesions are seen on blood smear and haemoglobin electrophoresis is the conclusive test [23]. In the case of macrocytic anaemia, vitamin B12 and folic acid levels should be determined first [23]. In vitamin B12 deficiency anaemia, reduced haemoglobin levels and increased MCV are often accompanied by thrombocytopenia and leukopenia.

In order to determine the cause of the deficiency, antibodies against lining cells and IF (intrinsic factor, Castle's factor) in serum are determined and gastroscopy with section collection for histopathological examination is performed. When normocytic anaemia is suspected, haemolytic anaemia should be confirmed or excluded. For this purpose, bilirubin, LDH, hap-toglobin and reticulocytes are measured, and blood smear, direct antiglobulin tests (DAT), indirect antiglobulin tests (IAT), direct agglutination tests (DAT) and Donath–Landsteiner tests (if biphasic haemolysins are present) are performed [8,23]. Normocytic anaemia may also accompany chronic diseases and endocrine disorders. The diagnostic assessment of ACD is based on a medical history of chronic diseases, e.g. RA, diabetes, SLE, renal failure and neo-plasm. The following elevated inflammatory parameters are indicative: CRP and/or ESR, along with changes in iron metabolism test results [23]. Finally, a bone marrow biopsy is sometimes necessary to diagnose and determine the cause of some anaemias, e.g. aplastic anaemia. [3].

Therapeutic transfusions in children with anaemia

Transfusions in non-adult patients are not only dependent on their clinical condition, but are particularly challenging mainly because of the wide variation in haematological, biochemical and immunological parameters between developmental periods. In the case of fetuses and neonates, the decision to undertake transfusion is based on the safety of the necessary transfusion. It is very difficult to establish universal transfusion guidelines for critically ill children, especially premature babies. Decisions made in transfusion practice usually depend on the patient's clinical condition and the clinician's skilled judgement [2].

For children under 4 months of age, and especially for preterm infants of low birth weight, the decision whether to perform a transfusion or not is based on the indications for transfusion given in Table 1 [24]. Newborns weighing less than 1500 g are those in whom the need for transfusions is greatly increased [25]. Bilirubin and Hb levels are strictly monitored in newborns. Bilirubin levels are responsible for brain damage from free bilirubin (known as kernicterus), and are therefore crucial in deciding whether to

carry out an exchange transfusion [26]. When deciding on a blood transfusion, it should be remembered that a transfusion of 3 mL of PRBCs/kg bw raises haemoglobin by approximately 1 g/dL and a transfusion of 1 mL of PRBCs/kg bw increases HTC by 1%. The recommended volume of transfused PRBCs should be 10-20 mL/kg bw (5-15 mL/kg body weight is recommended in premature infants and neonates). Larger volumes of 20-25 mL/kg bw may be required for haemorrhagic shock, major surgery and extracorporeal circulation [24,27-30].

Table 1. Indications for the PRBCs transfusion in preterm infants, newborns, infants under 4 months of age and children over 4 months of age [compiled from reference 24]

Indications for the PRBCs transfusion in preterm infants, neonates and infants under 4 months of age		
Age (in days)	Threshold HCT value and/or presence of risk factors	
1	<40%	Use of mechanical ventilation, FiO2>0.4 Life-threatening symptoms due to anaemia or hypovolaemia Planned surgical procedure
<15	<35%	
15-28	<30%	
>28	<25%	
Indications for the PRBCs transfusion in children over 4 months of age		
Pre-operative anaemia and HCT<24%; HGB<8 g/dL Loss of ¼ or more circulating blood volume Symptomatic anaemia and HCT<24%; HGB<8 g/dL Chemotherapy and/or radiotherapy, HCT≤24%; HGB≤8 g/dL Chemotherapy and/or radiotherapy, HCT≤30%; HGB≤10 g/dL Symptomatic anaemia in hereditary anaemias		

Red cell products (PRBCs) and whole blood for exchange transfusions in newborns are used to treat anaemia in fetuses, newborns, infants and children. The collection of these prod-ucts, as well as their preparation, storage and transfusion, should be carried out in accordance with current legislation. On the basis of these provisions, hospital procedures should be drawn up laying down the procedure to be followed in the event of the need for blood treatment [26,27]. Considering the recipients' low blood volume, low metabolic efficiency, higher haematocrit levels than in adults and immature immune system, products for these patients should be prepared in a special way. In the case of intrafetal transfusions and those intended for low birth weight preterm infants, irradiated components should be used and prepared in such a manner as to minimise the risk of cytomegalovirus (CMV) infection. Leukoreduction, i.e. the removal of leukocytes from donor blood components, is used or blood is selected from CMV-negative donors. Blood components with the shortest possible shelf life should be em-ployed for exchange transfusion. These components must ensure that the risk of metabolic and haemostatic disorders is kept to a minimum.

When preparing blood components for paediatric use, the number of contacts of the re-cipient with foreign antigens should be reduced as much as possible. Blood components are prepared by dividing one unit into smaller volumes. In some cases it is necessary to use leu-kocyte-depleted and/or irradiated components [31,43]. One element of ensuring transfusion safety is quality control of blood components, i.e. checking that the blood components received meet parameters of the standard. Controlled parameters include assessment of ABO and Rh blood group, presence of Treponema pallidum infection, tests for HbsAg, HBV DNA, anti-HCV p/c, HCV RNA, anti-HIV1/2 p/c, HIV RNA, unit volume, haemoglobin concentration, degree of haemolysis at final storage, haematocrit level and leukocyte count in the product. The therapeutic value of blood components depends primarily on their quality, and quality control of blood components is a process that indirectly verifies that all measures have been performed as intended [31,32].

Transfusions in fetuses and newborns

In the case of a fetus or a newborn, depending on their clinical condition, we can distin-guish between intrafetal, exchange and complementary transfusion. The choice of management for the above transfusions depends on the type of transfusion and on the immunohaematological findings of the mother and child [28].

Intrafetal transfusions

The most common causes of intrafetal transfusions are haemolytic disease of the fetus and newborn (HDFN), anaemia due to parvovirus B19 infection, congenital haemolytic anaemia, and bleeding in the fetus [33,34].

Haemolytic disease of the newborn is a syndrome of clinical manifestations occurring in newborns, and sometimes fetuses, as a result of maternal-fetal serological conflict. Such a conflict occurs when the child inherits an antigen from the father that the mother does not possess. After contact with the baby's blood cells, the mother has an immunological reaction to produce antibodies against this antigen. This in turn can lead to haemolysis of the baby's blood cells and consequently to anaemia [8]. The conflict may involve different red cell antigen systems. In the Caucasian population, immunisation of RhD negative women with the D antigen is the main cause of the HDFN development. The D antigen is the most immunogenic and can be found on fetal blood cells in the first weeks of fetal life. A limiting factor for immunisation may be concomitant conflict in the ABO system, when anti-A or anti-B antibodies from the mother neutralise fetal blood cells before they can elicit an immune response related to the D antigen. This situation can affect up to 20% of all infants. The incidence of HDFN caused by anti-D antibodies has been greatly reduced by the use of prophylaxis [35-37]. A serological conflict may develop between antigens of the Rh system other than the D antigen. It may also involve other red cell antigen systems such as Kell, Duffy or MNS. HDFN can also be caused by maternal anti-A and/or anti-B antibodies when the child has blood group A or B. However, the number of cases with clinically severe haemolytic disease due to conflict in the ABO system is low due to the fact that the antibodies of this system are mainly of the IgM class, and the A and B antigens are poorly developed on the red cells of the fetus [37-39]. The production of these antibodies begins in infancy and can sometimes be detected as early as three months of age. Antibody levels increase with age and are highest in young people [40].

The HCT value at which an intrafetal transfusion should be performed is Ht<0.25 between 18 and 26 weeks' gestation and <0.3 after 26 weeks' gestation. The desired haematocrit value amounts to 0.45. Transfusions are usually performed up to 34-35 weeks gestational age, after which the pregnancy usually ends at 36 weeks gestation. Transfusions are

carried out using a needle inserted into the umbilical vein under ultrasound guidance. Blood must be properly prepared before transfusion. Transfusion of blood immediately after removal from storage temperature (about 4 degrees Celsius) may result in fetal bradycardia [37,41]. After one or more intrafetal transfusions, the fetal circulation consists mainly of donor blood, as blood production by the marrow is suppressed and the remaining circulating red blood cells are destroyed. [42].

In the case of intrafetal transfusion, the tests to be carried out in the mother are, in par-ticular, ABO and Rh blood group determination, but also testing for the presence of alloanti-bodies in the serum (and, if present, their titre), determination of the D, C, Cw, c, E, e Rh an-tigens, the Kell K antigens, the Jka and Jkb Kidd antigens, the Fya and Fyb Duffy antigens, the S and s MNS antigens and the cross-check. In determining the titre, its effect on fetal anaemia is assessed [35,48]. Group 0 red cells containing no antigens to which the antibodies detected in the mother are directed, should be selected. If the blood group of the fetus is unknown or if there is an ABO incompatibility between mother and fetus, Irradiated Leukoreduced O RhD − Packed Red Blood Cells (PRBCs), which do not contain the antigens to which the antibodies of the mother are directed, are prepared for fetal transfusion. The blood group is verified in the donor. Cells that exactly match child's ABO blood type and Rh factor can be transfused into child's blood under the following conditions: ABO blood type of the fetus is compatible with that of the mother and the mother has AB type, whereas the fetus has A or B type. If there is a high incidence of antigenic conflict, it might be difficult to find cells that do not have the an-tigen responsible for alloimmunisation. Finding a donor among the mother's family is then advised. The donor search procedure should be initiated as soon as antibodies are identified. The donor of blood cells can be the mother under certain conditions. Among these, we can distinguish the formation of alloantibodies against a common antigen or the formation of an-tibodies with several specificities. The mother's blood is properly prepared, being deprived of the plasma in which the antibodies present are the cause of haemolytic disease of the fetus and the newborn (HDFN). After the end of pregnancy, transfusions continue according to the selection carried out during pregnancy [26,31,33,44-48].

PRBCs for intrauterine transfusion should be leukocyte-free and treated with γ or X-rays. PRBCs of a specific phenotype, stored for no more than 5 days, shall be used to prepare the component. Leuko-reduced PRBCs are obtained by removing most of the leukocytes and platelets by filtration. It should contain less than 1x106 white blood cells/unit. The PRBCs used are those from which leukocytes have been removed within 48 hours of collection, but it is recommended that leukocytes be removed within 24 hours. The next component is then irra-diated. It consists in exposing the PRBCs to ionising radiation (25-50 Gy). This act is designed to inhibit the proliferative capacity of lymphocytes. Before irradiation, a special radiosensitive label that changes colour or appearance under the influence of γ or X rays should be applied to the container. If a component is made from maternal blood, an equivalent volume of 5% albumin solution or 0.9% NaCl solution must be added before centrifugation and the erythrocytes must then be suspended in 5% albumin solution or quarantined/inactivated AB plasma. 0.9% NaCl solution is not used due to the risk of sodium-potassium imbalance. The haematocrit should be in the range 0.70-0.85 and the volume should be in accordance with the requirements of the contracting authority.

The resulting product should be labelled with: the name of the centre where the component is obtained, the name of the component, the ABO and RhD blood group, the component number (corresponding to the donation number), the volume in mL, the haematocrit value, the name of the anticoagulant and/or enrichment solution, the date of collection, the date of preparation, the expiry date and time and information on the results of additional tests, including other labelled red cell antigens. The label should also contain additional comments, i.e.: 'Store at 2°C to 6°C', 'Do not transfuse if haemolysis, damage to the container or other changes to the preparation are observed', 'Transfuse immediately after receiving through a 170-200 m filter'. After irradiation, a component shall be labelled with information on the irradiation and it can be stored up to 24 hours [31,48].

Exchange transfusions

After birth, the connection to the maternal circulation is severed and the risk of hyper-bilirubinemia in neonates is significantly increased due to the immature development of the metabolic pathway that breaks down bilirubin in the neonatal liver. Treatment of hyperbiliru-binemia is crucial in the neonatal period due to the risk of bilirubin-induced encephalopathy [49]. Exchange transfusion is indicated in case of critical bilirubin levels [50]. The mandatory tests prior to maternal exchange transfusion are ABO and Rh system determination, an alloantibody test and a cross-matching. The child also undergoes ABO and Rh system determination, a cross-matching and, additionally, a direct antiglobulin test (DAT). If the DAT is positive and maternal serum is not available, a blood cell eluate is performed to identify the antibodies. The donor's blood group is also verified.

The choice of blood for exchange transfusion depends on whether the newborn has had an intrafetal transfusion, and whether there is ABO compatibility between the baby and the mother or not. It is impossible to identify the newborn's blood group in cases of prior intrafetal trans-fusions. In these cases, the same blood as during the intrafetal transfusion is administered. If there has been no intrauterine transfusion, and there is ABO compatibility between mother and child, compatible PRBCs (wherein there is an exact match for ABO type and Rh factor) supplemented with plasma that exactly matches the child's blood type and Rh factor or AB plasma are transfused into the child's blood. If there were no intrauterine transfusions and there is an ABO incompatibility between mother and fetus, O RhD PRBCs exactly matching the baby's blood type and Rh factor supplemented with plasma that is compatible with the baby's blood or AB plasma, are transfused. If we additionally find no anti-A or/and anti-B antibodies in the mother's serum, the PRBCs are transfused as in the case when there is ABO compatibility between mother and child [28,48].

In serological conflicts regarding other antigens, red cells prepared for transfusion must not contain the antigen responsible for maternal immunisation. As with post-fetal transfusion, when there is a high-incidence antigen conflict, difficulty in finding a donor is to be expected. In this case, it is advisable to look for a donor among the family. The donor can also be the mother, provided that the plasma with antibodies is removed [51]. Affected infants may require phototherapy to oxidise unbound bilirubin so that it can be excreted in the urine. In patients diagnosed with fetal haemolytic disease, close monitoring of bilirubin and haemoglobin levels is justified [52,53].

Leukoreduced whole blood (LR-WB) or leukoreduced packed red blood cells (LR-PRBCs) suspended in fresh frozen plasma (FFP) are used for exchange transfusion in neonates. The choice of blood for exchange transfusion is determined by the antibodies pro-duced by the mother, so a component must be prepared from blood with a specific phenotype. Usually transfused are group 0 cells with low antibody titres, RhD negative or RhD blood identical to the newborn, Kell negative and negative for the antigen to which the mother has developed antibodies. LR-WB collected on CPD (Citrate Phosphate Dextrose) and previously stored for no more than 5 days is used. The preparation method is based on subjecting the selected WB unit to filtration to deprive it of leukocytes and irradiating it. The removal of leukocytes should take place no later than 48h after sampling, but it is recommended that this be done within 24h. The HCT should be in accordance with the requirements of the contacting authority. If there is a need to dispense blood with an increased HCT value, what volume of plasma needs to be removed is calculated and then the blood product is centrifuged until the desired HCT is achieved. The component shall be labelled with the required information. As with LR-PRBCs for post-irradiation intrafetal transfusion, the resulting whole blood product must be labelled. It can be stored for 24 h after irradiation [26,31].

Reconstituted whole blood (RWB), i.e. LR-PRBCs suspended in fresh frozen plasma (FFP), can also be used for exchange transfusion. RWB is obtained by suspending usually group O red cells in AB plasma or identical plasma to the recipient's blood group. In haemolytic disease of the newborn, RWB should be prepared from red cells of a specific phenotype. This is done by using PRBCs that have been stored for up to 5 days and thawed FFP that was previously inactivated or quarantined. Leukocytes are removed from the selected PRBCs by filtration. It is recommended to remove leukocytes within 24 hours of donation. If this is not possible, it is acceptable to use the component from which the leukocytes were removed at a later date, but not exceeding 120 hours of donation. The HTC should be in the range 0.40-0.50. The container with LR-PRBCs should be centrifuged and the supernatant removed. The next step is to suspend the obtained product in previously thawed AB plasma or plasma that exactly matches the recipient's blood group. The reconstituted component shall be irradiated. It is recommended to perform preparatory procedure in a closed system. A new component number taking into account the numbers and groups of both components of the product shall be included on the label. The red cell phenotype should also be stated if other than anti-D antibodies are found in the mother. All required information must be included on the label as for other blood components. After irradiation, the product must be labelled with the information that it contains an irradiated component. If the ingredient was prepared in a closed system, it can be stored up to 24 hours. If it was prepared in an open system, storage time is reduced to 8 hours [31,41].

It can now be seen that the number of exchange transfusions that are performed to new-borns is decreasing. This is due to the fact that pregnant women receive better care during pregnancy and after delivery. Immunoprophylaxis of HDFN by administration of anti-D IgG and by monitoring of pregnancy and, if necessary, by intrauterine transfusions is given [26]. Early total exchange transfusion is performed when indirect bilirubin levels in cord blood exceed 5 mg/dL, haemoglobin levels are below 10-11 g/dL or when there are signs of impaired blood oxygenation. The purpose of this transfusion is to slow the build-up of plasma bilirubin and to compensate for anaemia. Antibody-coated red cells, excess bilirubin and free antibodies in the plasma are removed. Late exchange transfusions are used when bilirubin levels rise at a rate of 0.5-1 mg/dL/hr or exceed 20 mg/dL in conjunction with a decrease in HTC [50,54].

Complementary transfusions

Neonates and infants with HDFN often require a supplementary blood transfusion if not accompanied by severe hyperbilirubinemia [50,54]. In complementary transfusions in neonates and infants up to 4 months of age, irradiated, lekocyte-poor blood is chosen. In such young children, the choice of blood for the first transfusion continues with further transfusions until they are 4 months old. In the baby's mother, the basic tests performed are ABO and RhD de-termination and alloantibodies test. ABO and Rh are assessed and DAT is performed in the child. If there is a positive DAT, an eluate from the newborn's blood cells is produced and tested for antibodies. When maternal blood is not available, the serum is tested for immune antibodies. The blood group is determined in the donor. When immune antibodies are detected in the mother's serum and/or the direct agglutination test is positive in the child, a compatibility test is carried out. The compatibility test is performed with maternal serum. Naturally, blood without the antigen to which the mother has developed antibodies is selected. However, if no immune antibodies are found in the mother's serum and the baby's DAT is negative, the donor's blood group is verified without performing a compatibility test. The choice of blood for transfusion depends on the ABO blood group compatibility between mother and child. The same blood product continues to be administered to the neonate after fetal transfusion [26,28,34,48].

LR-PRBCs are used in neonatal complementary transfusions. ABO and RhD red cells that exactly match the baby's blood are the component unless antibodies are found in the mother's blood that indicate the need for a different blood group. PRBCs for neonatal transfusions need to be deprived of leukocytes by filtration and usually irradiated. The component is prepared using phenotype-specific PRBCs. PRBCs are used with any preservative fluid: CPD (Citrate Phosphate

Dextrose), CPDA-1 (Citrate, Phosphate, Dextrose, Adenine), SAGM (Saline, Ade-nine, Glucose, Mannitol). Any such fluid should be stored for no more than 48 hours before leukocyte removal, and leukocytes should be removed within 24 hours of donation. If this is not possible, the component from which the leukocytes were extracted later may be used within 120 hours of donation. To reduce the recipient's exposure to the risk of infection transmission, after leukocyte removal, it is recommended to divide a unit of red cells from a single donor into 3 to 8 portions in a closed system. It is also recommended that the component be irradiated immediately before issuing the product. Only those PRBCs which have been stored for no more than 14 days may be irradiated. After irradiation, the component can be stored up to 48h. Spe-cial requirements may be necessary in certain situations. In such cases, the doctor should specify these requirements when ordering the blood component. The label shall also contain all the required information, as for the other components [24,31].

Paediatric transfusions

Transfusions in older infants over 4 months of age and in children are rarely performed. Paediatric transfusions affect particularly children in ICUs after surgical procedures (cardiac and neurosurgical procedures have an increased risk of bleeding), with diseases such as tha-lassaemia, with oncological diseases, during and after intensive chemotherapy or radiotherapy [34]. The principles of blood treatment in children are similar in many respects to those used in adults, but there are also significant differences that need to be considered when making a decision about transfusion. The key issues in paediatric transfusion are the appropriate selection of blood component and the establishment of thresholds that are indicative of transfusion [19]. In terms of selection of an appropriate product, the following are used for paediatric patients: buffy coat-free PRBCs, buffy coat-free PRBCs in enrichment solution or LR-PRBCs divided into 25-100 mL portions. For paediatric portions of whole blood or PRBCs, the storage period shall not exceed 35 days provided that they have been prepared in a closed system. Opening the system shortens the expiry date to 8h. The resulting portions shall be appropriately labelled, including all divisions in the letter/number designation of the blood component: first division with the letters A, B, C, D and if further subdivided, the letters ‘a’ and ‘b’ shall be included as well. Additional steps such as irradiation or washing of the component are required in some situations. Irradiation prevents transfusion-associated graft-versus-host disease (TA-GvHD). Children with immune system failure and acute immunodeficiency syndrome are particularly vulnerable. The purpose of washing is to remove plasma proteins or anticoagulant contained in the preservative fluid, thus reducing the risk of allergic reaction. Washing the component shortens its validity to 8 hours [26,31,55].

Determining the thresholds that constitute an indication for transfusion is not easy. The decision to transfuse blood is influenced by the type, severity and causes of the anaemia, as well as the course of the disease and the patient's clinical condition – symptoms such as tachypnoea, tachycardia, poor weight gain, decreased physical activity should not be neglected. Threshold values indicating the use of complementary transfusions in some diseases can be found in the literature: patients with congenital spherocytosis Hb<7 g/dL, thalassemia patients with Hb concentration <6 g/dL, AIHA patients with Hb<5-6 g/dL, patients with sickle cell anaemia that have haemoglobin concentration <4.5-5.0 g/dL (in these patients, Hb after transfusion should not exceed 10 g/dL), children with oncological diseases with haemoglobin level <7-8 g/dL, patients in intensive care units, haemodynamically stable Hb<5 g/dL. The definition of indi-cations for massive transfusion in children is based on the experience of adult patients: blood loss of 80 mL/kg bw/24h, 40 mL/kg bw/3h or 2-3 mL/kg bw/min [20,41,56,57].

For children over 4 months of age, a confirmed child's blood group result, a compatibility test and verification of donor blood are required prior to blood transfusion. Depending on the result obtained, clearly defined procedures should be followed. This is necessary to ensure patient safety and to eliminate possible post-transfusion reactions [28,34].

In the case of haemoglobinopathies, congenital dyserythropoietic anaemias, aplastic anaemia or other chronic conditions with anaemia and requiring frequent blood transfusions, it is recommended to determine the phenotype/genotype of the red cells and use phenotypically compatible products. This reduces the risk of developing immune antibodies [41].

Autoimmune haemolytic anaemia (AIHA) in children, more often than in adults, results in a rapid course of haemolysis of the blood cells, which may necessitate transfusion of the PRBCs. The tests needed in this case are the same as in adults. Serological compatibility test in patients with autoantibodies is complicated. Elution of autoantibodies from red blood cells should be performed to confirm their presence. The patient's serum/plasma is also tested for the presence of autoantibodies. The selection of blood for transfusion for patients with warm-type AIHA is particularly challenging and has a higher risk than for other recipients, because autoantibodies generally mask the presence of alloantibodies. Adsorption of free autoantibodies is performed for this purpose [8,37].

Children treated with blood components and blood products are particularly vulnerable and require specific criteria to be met. If they receive blood transfusions, they often occur multiple times, and it is therefore of particular importance to prevent adverse transfusion reactions with long-term consequences. To increase transfusion safety, all transfusion management require-ments must be strictly adhered to. Only blood and blood components from selected donors tested to be free of blood-borne viral infections and red cell products tested for compatibility should be transfused. Blood transfusion should be documented. Before treatment, information on the product label and the result of the compatibility test must be checked. Blood and blood components are transfused using disposable sterile equipment. As whole blood and PRBCs are stored at low temperatures (2-6°C), the blood should be warmed before transfusion. The blood warming process should also be monitored and carried out only in a special device equipped with a thermometer and an alarm system. This procedure is recommended for children if the transfusion rate exceeds 15 mL/

min and for exchange transfusion in neonates. Transfusion of blood or blood components must be started within 30 minutes of dispensing. The transfusion time for a whole blood unit or PRBCs must not exceed 4 hours. PRBCs/LR-PRBCs transfusion rate of 5 mL/kg bw/hour is considered safe. Patient observation is required both during and after transfusion. It is advisable to measure the patient's basic vital signs: body temperature, HR, BP [20,41,51,55].

Complications after transfusion of blood and blood components

Any transfusion may result in a variety of post-transfusion reactions, immunisation or transmission of infectious diseases, therefore, the decision to transfuse blood or blood com-ponents should be made when the patient cannot be treated effectively in any other way and the expected benefits of the transfusion outweigh the risks of possible complications [19,55,58,59].

Post-transfusion complications include early complications that occur up to 24 hours after or during transfusion and late complications that may occur more than 24 hours after transfusion. Early post-transfusion reactions are divided into immunological: acute haemolytic reaction, anaphylactic reaction, transfusion-related acute lung injury (TRALI), allergic reaction, febrile non-haemolytic transfusion reaction; and non-immunological: post-transfusion sepsis, transfusion-associated circulatory overload (TACO), hypothermia, hyperkalaemia, hy-pocalcaemia, hypomagnesaemia, non-immune haemolysis, air embolism, ACE inhibi-tor-associated hypotension and transfusion pain. Late post-transfusion complications can also be divided into immunological and non-immunological according their origin. Immunological may include alloimmunisation, transfusion-associated graft-versus-host disease (TA-GvHD), transfusion-related immunomodulation (TRIM), delayed haemolytic transfusion reaction (DHTR), post-transfusion purpura. Non-immunological may include haemochromatosis and transmission of infectious agents [50,58].

Blood transfusion carries the risk of pathogen transmission: HCV, HBV, HIV, EBV, toxoplasmosis, malaria, syphilis, brucellosis and tuberculosis. This is due to the so-called 'se-rological window', i.e. the period between the donor's infection and the appearance of infection markers in his blood. This is also due to fact that detecting the disease during this time is im-possible [55,60]. Blood-borne pathogens also include Cytomegalovirus (CMV) or protozoa of the genus Babesia [61-63]. Extravectorial babesiosis infection through blood products is not fully understood. Survival ability of prioplasmas in erythrocytes outside the host organism is high [64,65]. Despite cryopreservation of blood products and radiation, Babesia parasites re-main viable [66,67]. There is also a potential risk of transmission of emerging pathogens e.g. Zika virus [68]. Three probable cases of Zika virus are known, but they are associated with transfusions of PC (platelet concentrate) [69].

Non-infectious serious hazards of transfusion (NISHOTs) are usually complications fol-lowing transfusion of blood products in neonates. In neonatal intensive care units, necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular haemorrhage (IVH) and abnormal development of the nervous system have been observed most frequently [60,29]. Necrotising enterocolitis (NEC) particularly affects extremely low birth weight (ELBW) neonates and 5% of neonates born prematurely. Packed red blood cells (PRBCs) transfusion has been implicated as a predisposing factor in the development of NEC, which can result in the development of transfusion-associated NEC (TANEC) within 48 hours of transfusion. It was reported that TANEC symptoms were more severe than those of NEC, mostly required life-saving surgical intervention and were therefore associated with high mortality [30].

CONCLUSION

Blood transfusion is a widely-acknowledged method of anaemia treatment. Blood and its components are transfused to replenish circulating blood volume, maintain the oxygen capacity of the blood and normalise the function of the coagulation system. Severe anaemia causes global tissue hypoxia and lactate acidosis. The sudden loss (more than 30%) of circulating blood exceeds the body's compensatory capacity – leading to hypovolemic shock – and requires immediate blood treatment. For the treatment of haemolytic disease of the fetus and newborn (HDFN), exchange transfusion is performed to prevent bilirubin encephalopathy. Blood is indispensable in a life-threatening emergency, but it also comes with its own set of risks, just like any drug. Therefore, careful donor selection and continuous improvement of blood collection and processing methods are extremely important. Thanks to the development of modern transfusiology, it has become possible to use blood components according to the individual needs of the patient. Whenever possible, only those components whose absence is the cause of the disease symptoms should be transfused. When deciding on transfusion, not only the hae-matological indices, but also the patient's clinical condition should be assessed. Children are a particularly vulnerable group and require specific criteria. This is mainly because of the fact that their physiological and haematological systems are different from those of adults [19,55,58].

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