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# Персонализиран трансфузионен подход – какво да знаем и защо се нуждаем?

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# Personalised transfusion approach – what do we need to know and why do we need it?

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**РЕЗЮМЕ:**

Персонализираният трансфузионен подход е основа за безопасна ефективност на кръвопреливането. Непрекъснато се увеличава броя на новооткрити кръвногрупови антигени, установяват се нови антиеритроцитни антитела, за които не сме подозирали, а това е предизвикателство пред клиницист и пред трансфузионната медицина като цяло. Навлизането на нови терапии, които водят до промени в имунохематологичния статус, налагат съобразяване с индивидуалните особености на рискови групи реципиенти. Клинично значим е персонализирания подход при родилки, новородени и тези, чийто алгоритъм на лечение включва алогенна трансплантация на хемопоетични стволови клетки. Както са важни молекулярните (генетични) изследвания на дарители,

**ABSTRACT:**

The personalized transfusion approach is the basis for safe and effective blood transfusion. The number of newly discovered blood group antigens is constantly increasing, new anti-erythrocyte antibodies are being identified that we did not suspect, and this is a challenge for the clinician and for transfusion medicine as a whole. The introduction of new therapies that lead to changes in the immunohematology status require consideration of the individual characteristics of risk groups of recipients. The personalized approach is clinically significant for postpartum women, newborns and those whose treatment algorithm includes allogeneic transplantation of hematopoietic stem cells. Just as molecular (genetic) studies of donors and recipients are important, so is the minimization of all possible risks of blood transfusion. The main indi-

реципиенти, така е важна и минимизацията на всички възможни рискове от кръвопреливане. Основните индикации за вида на необходимата кръвна съставка зависят и от фактори, свързани със самия пациент, обем и продължителност на трансфузионната терапия. През последните години персонализирания подход навлезе и при производството на кръвни

съставки, което би позволило максимално удължаване на срока на съхранение или превенция на инфекции чрез патогенна инактивация.

**Ключови думи:** персонализирана трансфузионна медицина, трансфузионна стратегия, генотипизиране и бременност, алогенна трансплантация на хемопоетични стволови клетки

cations for the type of blood component needed also depend on factors related to the patient himself, the volume and duration of transfusion therapy. In recent years, the personalized approach has also entered the production of blood components, which would allow for maximum extension of shelf life or prevention of infections through pathogen inactivation.

**Key words:** personalized transfusion medicine, transfusion strategy, genotyping and pregnancy, allogeneic hematopoietic stem cell transplantation

**Introduction:**

The personalized transfusion approach involves molecular testing of genes encoding clinically relevant antigens. As a result, donor antigens can be targeted by the recipient's immune system, since the two systems are not genetically identical and it is impossible to match all blood group systems. The first gene encoding the expression of blood group antigens, molecularly cloned and sequenced (Siebert PD, et al.) as early as 1986, was the MNS system gene. [1]. Avent ND et al. described the RHCE and RHD genes responsible for encoding Rh antigens in 1990 [2]. By genotyping (molecular testing) of blood groups, now is possible to determine the phenotypic expression with a high degree of probability. The use of blood group genotyping in fetal medicine is of high clinical significance, allowing us to assess both the risk of hemolytic disease of the fetus and whether there is an indication for prophylaxis with anti-D immunoglobulin in Rh D (-) negative pregnant women. Genotyping is only able to distinguish between variants of the D antigen (weak or partial D), where serological methods have only proven attenuated expression (weak D). This is evidence that in pregnant women who have a variant of the D antigen, but without the risk of the formation of anti-D antibodies in a D (+) positive fetus, prophylaxis with anti-D immunoglobulin is not necessary. In addition, monoclonal antibodies, such as anti-CD38 (daratumumab), are used to treat various hematological diseases (like multiple myeloma) leading to a positive indirect antiglobulin test in the screening for antierythrocyte antibodies. In this case, an individual transfusion approach is required, which depends on age, disease, alloimmunization risk, in order to avoid post-transfusion complications. It is extremely important to know where and when we need to genotyping blood groups in recipients, especially when this is not a routine examination for blood donors and/or recipients. The personalized transfusion approach is expressed not only by molecular (genetic) blood group testing, but is also characterized by an individual transfusion policy, which is tailored to the age, diagnosis, volume of transfusion therapy required for the specific patient, as well as whether allogeneic hematopoietic stem cell transplantation will be used as part of the course of treatment.

**1. Blood donors and blood components**

Not only donor selection and screening for transmissible infections are responsible for the safety of blood transfusion, but also other key factors. One of them is the storage period, as a number of studies have been focused on the damage that occurs during the storage of

blood components, another important factor as an additional prevention regarding the safety of blood is the introduction of pathogenic viral inactivation. Yoshida, T et al. clarified various reasons that lead to damage during storage [3], and Belpulsi D, et al. through studies gave us an answer whether the transfusion of blood that is at the end of its shelf life has a role in the final result of the hemotransfusion performed [4]. D'Alessandro A, Liumbruno G. have not identified any other factor that, apart from the age of the blood, has a leading role in the good clinical outcome in the recipient [5]. From the study by Lanteri, Kanias, Keating, et al. phase of the REDS-III RBC-Omics study back in 2018 [6] it was found that in leukocyte-depleted erythrocyte concentrate hemolysis (spontaneous, oxidative) is correlated with the processing methods used, and increases during storage, unlike mechanical or osmotic hemolysis, which do not change their degree. They prove the role of biological factors of the blood donor for the sensitivity of erythrocytes to hemolysis in vivo, but the influence of genetic characteristics cannot be ruled out. Tsang HC, et al. published that in transplantology, and especially in organ transplantation, genotyping of blood donors and recipients can answer questions about various complications, considering for example that passenger lymphocyte syndrome [7], is a complication that has been found in ABO mismatched organ transplants with a reported frequency - in renal (10%), liver (40%) and heart-lung transplants (70%). There are cases in which post-transplant hemolysis can be extremely difficult to control despite the use of immunosuppression.

In blood donors with extremely rare blood groups, genotyping may be the only option for transfusion therapy in recipients who have the same rare phenotype. Gong, Xu, Zhu [8] through DNA sequencing of 277 foreign blood donors have managed to create a DNA database with rare blood groups, the database has been compared with the international blood group gene database (BGMUT), and some of the units of these blood donors have been frozen, including the effect after their clinical use has been monitored. Regional and ethnic features are correlated with the polymorphic characteristics they have established.

At this stage of the development of medicine, 48 blood group systems have been proven [9], but with the help of blood group serology, a small part of these antigens are proven, as a result of which it is not excluded that the transfused blood components contain new antigens or antibodies. The 48th proven by Tilley LA, et al. newly defined blood group is MAL [10], whose antigen is AnWj. Only one person in the world has a proven Gwada-negative phenotype [11]. Thus, in the International Society of Blood Transfusion (ISBT) the registered and proven blood group systems are currently 48. For this reason, Khillan, Kamini and Ranjan, Vivek [12] shared the opinion that the "mystery blood groups", discovered lately, oblige us to apply best transfusion practices, so that unproven antibodies do not cause serious consequences, because no one has thought to look for such a cause. By genotyping blood donors, it is now realistic to provide antigen-negative blood, especially in immunized patients with a combination of different specificities, which are a challenge for the transfusionist and the clinician. In addition to assessing the risk to the fetus, NGS technology is part of the studies in blood donor screening.

**2. Neonates**

The most fragile age of patients in transfusion therapy are newborns, who require an individual approach that is consistent with their physiological and immune system characteristics, which are significantly more specific than those of adult recipients. Shafique et al. draw attention to the fact that the type and volume of blood transfusion depends on their gestational age, birth weight, peripheral hematological indicators, but the most significant is the prevention of complications from blood transfusion [14]. What approach will be chosen - a restrictive or liberal transfusion strategy, especially if it concerns premature birth, is a question whose solution is determined by the individual needs and clinical characteristics of the newborn. The volume of blood transfusions is recommended to be no more than 30 ml, in order to avoid liver damage when the newborn's weight is low [14].

Hoppe et al. [15] proved that if erythrocyte concentrates are irradiated after the 8th day of blood donation, the K+ level increases, the degree of hemolysis increases, therefore they recommend that irradiation be before the 8th day of blood collection, the storage of this blood can be extended by another 48 hours, but only with washed erythrocytes. The recommendations require that the irradiated blood be transfused within 24 hours of the procedure. When massive blood transfusion is required in neonatology, it is crucial to monitor the K+ level to avoid the development of hyperkalemia, which is a result of the transfusion of red blood cell concentrate. Guidelines (Guidelines on irradiation of blood components produced by the Australian and New Zealand Society for Blood transfusion) listed the factors that require the transfusion of irradiated blood components in the neonatal period, with the first being previous intrauterine blood transfusion, followed by cardiac surgical interventions, when an immunodeficiency state is established, and also in all cases where the donor of the blood component is a related donor [16]. Whyte and Jefferies in 2014 [17]. in the guidelines for blood transfusion they have emphasized that newborns who are not of blood group O, in whom there is no evidence of passively transmitted anti-A or anti-B antibodies from the mother, can be transfused isogroup - with ABO identical blood, but in accordance, without the risk of immunization, with the Rh phenotype of the baby. It is extremely important for the newborn period to ensure maximum safety and security of blood components in order to avoid the occurrence of any possible complication.

### 3. Pregnancy

Molecular (genetic) testing is the leading method for assessing the risk to the fetus in the presence of allo-antierythrocyte antibodies during pregnancy. In in vitro fertilization procedures, the inclusion of genotyping is part of the preimplantation prevention of hemolytic disease of the fetus or newborn, especially in an alloimmunized pregnant woman whose partner is a heterozygous carrier of the allele encoding the antigen to which the antibody is directed. Daniels G. specifies that embryos are genotyped, and those that are assumed not to possess the relevant antigen that is at risk for hemolytic disease are selected for implantation [18]. However, it is possible to obtain a false negative result, the cause of which is fetal DNA that is below the relevant detection threshold in the maternal plasma. Haimila K. published that testing after 10-12 weeks of gestation yields more accurate results, especially for antigens that are not RhD [19]. Prevention of alloimmunization in women begins with an individual transfusion approach in case of need for blood transfusion for any reason, starting from early childhood. Genotyping is not only a non-invasive method during pregnancy, but in pregnant women with alloimmunization it provides an extremely accurate assessment of the degree of risk to the fetus.

### 4. Pathogen virus inactivation in transfusion medicine

As additional blood safety measures regarding pathogens transmitted by blood transfusion, these are bacterial screening and pathogen inactivation. Pathogenic viral inactivation of blood components is part of the individual transfusion approach in transfusion medicine for various reasons:

1. Piccin, A. et al. reported that it has not been introduced as a routine procedure in the world to prevent the risk of new or known pathogens, such as West Nile Virus, Zika, MERS, SARS, Malaria, and others. Also, in blood donors with false negative samples, but who are potentially infectious, with pathogen inactivation they will be inactivated [20]
2. In addition, it has not been proven that donor antibodies are neutralized in the donor's plasma, which allows the available ready-made donor antibodies to be used for new infectious agents.
3. Despite mandatory donor screening using NAT technology for HBV, HIV and HCV, the risk of transmission of infections by bacteria, protozoa and other emerging pathogens is not eliminated.
4. Maximum safety of blood products can be achieved with the help of additional bacterial screening or various pathogen reduction (PR) technologies.

The procedure also appears as an alternative to the irradiation of blood components, thus, in addition to the main goal - prevention of TA-GvHD, prevention of the risk of transmissible infections is achieved. The pathogen inactivation technology allows to extend the shelf life of platelet concentrates, which are the most labile blood component with the shortest shelf life - only 5 days. Results of a Randomized, Controlled Phase III Trial Transfusion Efficacy and Safety of Amustaline/Glutathione Pathogen-Reduced Red Blood Cells by Richard J Benjamin et al. [21] are without differences in the final result of the transfusion of erythrocyte concentrates with and without PR in cardiac surgery. In patients with allogeneic stem cell transplantation who have received stem cells from a cytomegalovirus (CMV) negative donor, if they receive PR platelet concentrates, they will receive not only CMV negative platelets, but also an alternative to irradiated platelets. According to literature data, a study by Castro, G. et al. on the effect of PR as an alternative to irradiation, has found that the effectiveness in inactivating T-lymphocytes is higher than the irradiation procedure [22]. Let us not forget the palette of indications for transfusion of irradiated blood components: first of all, intrauterine transfusion, if necessary neonatal exchange transfusion, immunodeficiencies, in autologous and allogeneic stem cell transplantation with the corresponding period of transfusion of irradiated blood components, as well as CAR-T therapy (7 days prior to collection and 3 months post-infusion), Hodgkin lymphoma, therapy with purine analog, antithymocyte globulin, alemtuzumab [20]. de Martel C. and co-authors published in 2018 that 13% of cancer incidence worldwide is also associated with infections [23].

**5. Allogeneic hematopoietic stem cell transplantation**

According to L.S. Williams et al. the possible rate of disease recurrence after transplantation is 30%, of which 2-5% is malignant, but of donor origin [27]. Malignant disease of donor origin may be associated not only with clonal hematopoiesis of the donor, but also with a genetic predisposition allele of his germline. There is no evidence in the literature for genetic sequencing of donors, related or unrelated, before allogeneic transplantation. A donor who does not have a genetic abnormality, given the possibility of such a choice, is also important for the final outcome in such a high-tech procedure as allogeneic stem cell transplantation.

The personalized transfusion approach starts with the blood donor, goes through strategies for the production of blood components, in order to achieve the best result of blood transfusion for the patient. A personalized approach in transfusion medicine is not only molecular (genetic) testing, but also the best specific transfusion program for the specific patient with management not only of post-transfusion complications at the given moment, but also of possible future consequences of a previous blood transfusion. The most vulnerable groups and patients most in need of an individualized transfusion strategy based on evidence are newborns, children, pregnant women and transplant patients. Genotyping in blood group serology plays a leading role in fetal medicine, in complicated cases where standard immunohematology tests are not sufficient and we need additional studies to prove blood group antigens. The choice of the best transfusion policy starts from the diagnosis, but always tailored to the individual characteristics of the specific patient. The College of American Pathologists has indicated that various developments to achieve universal blood continue, the leading goal of which is to have the possibility of overcoming challenges in the case of an insufficient number of blood donors, because the example of the COVID-19 pandemic has led to an insufficient amount of 150,000 red blood cell (RBC) units according to the American Red Cross (ARC) [28]. D'Alessandro, A. describes that omic technologies, which are a tool for the best strategies in processing, achieving the best storage conditions at the best quality of blood components, but tailored to the recipient, are an opportunity to understand the biology of donors and recipients [29]. Through omics technologies (genomics, transcriptomics, proteomics, metabolomics) biology can become clearer in the scope of personalized

medicine. What we need to know to apply the highest individual quality in transfusion medicine depends on what we need to achieve the management of each risk. According to D'Alessandro, A., the advent of artificial intelligence can show us the way for which is the best personalized transfusion approach, but by comparing the clinical characteristics of donors and recipients [30].

In conclusion, the future of transfusion therapy is the alternative to human blood, but until the time of universal blood arrives, we need a personalized (individual) transfusion approach for both the recipient and each unit of donated human blood.

Clinical Hematology International (Adkins BD et al.) emphasize that the personalized transfusion approach in patients with allogeneic hematopoietic cell transplantation should be consistent with the fact that erythroid engraftment occurs 3-4 weeks after transplantation, while platelet engraftment occurs approximately 2 weeks later [24]. Prevention of alloimmunization to erythrocyte antigens (outside the ABO system) is important both for reducing the risk of posttransplant hemolysis and for possible prolonged reticulocytopenia, if in this particular case the donor possesses the corresponding antigen. In allogeneic transplantations, when the donor and recipient do not allow for a coincidence of the transfused blood with both Rh phenotypes in terms of Rh system antigens, then in this case we mean the period of erythroid engraftment. In the first weeks after transplantation, it is safer for transfusion therapy to include erythrocyte concentrates, the phenotype of which matches that of the recipient. Tay, J. and colleagues in their study [25] found that the restrictive transfusion strategy is not different from the liberal one in terms of effectiveness, but it allows to reduce the transfusion of allogeneic blood in this type of transplantation, which, however, is of key importance in recipients with rare blood groups and phenotypes. According to Saris A, et al., the question of whether pathogenically inactivated platelet concentrates are a better choice in these patients is unresolved, because any loss of platelets as a result of additional processing may have an effect on the corrected increase in platelet count and the processes of HLA alloimmunization [26].

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# Ранна диагноза на остра мезентериална исхемия: интегрирани образни и лабораторни подходи

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# Early diagnosis of acute mesenteric ischemia: integrated imaging and laboratory approaches

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**РЕЗЮМЕ:**

Острата мезентериална исхемия (ОМЕИ) е животозастрашаващо състояние, при което ранната диагноза е от решаващо значение за намаляване на смъртността. Интегрираните образни и лабораторни подходи играят ключова роля в този процес. Многодетекторната компютърно-томографска ангиография е златен стандарт в образната диагностика. Тя позволява визуализация на тромбоза, емболия и исхемични промени в чревната стена. Допълнителните образни методи като дуплексната ехография са ценни при пациенти с противопоказания за приложение на контраст. Лабораторните маркери допълват образната диагностика. Повишените нива на серумния лактат показват тъканна хипоксия. D-димерът също е полезен маркер за изключване на тромбоза.

**ABSTRACT:**

Acute mesenteric ischemia (AMEI) is a life-threatening condition where early diagnosis is critical for reducing mortality. Integrated imaging and laboratory approaches play a key role in this process. Multidetector computed tomography angiography is gold standard in imaging diagnosis. It allows visualization of thrombosis, embolism, and ischemic changes in the bowel wall. Additional imaging methods such as duplex ultrasound are valuable in patients with contraindications to contrast. Laboratory markers complement imaging diagnosis. Elevated serum lactate levels indicate tissue hypoxia,. D-dimer is also a useful marker for ruling out thrombosis. The combination of imaging methods and laboratory indicators enables early detection of the disease, even before irreversible ischemic changes occur. This paper presents an up-to-

Комбинацията от методи за образна диагностика и лабораторни показатели позволява ранно откриване на заболяването, дори преди да настъпят необратими исхемични промени. Тази статия представя актуален преглед на съвременните интегрирани подходи за ранна диагностика на ОМЕИ и подчертава значението на мултидисциплинарния подход за подобряване на резултатите при пациентите.

**Ключови думи:** остра мезентериална исхемия, образна диагностика, лабораторни подходи

date review of modern integrated approaches for early AMEI diagnosis and emphasizes the importance of a multidisciplinary approach to improving patient outcomes.

**Key words:** acute mesenteric ischemia, imaging, laboratory approaches

## Introduction

Acute mesenteric ischemia (AMEI) is a relatively rare but extremely dangerous condition, with an incidence of approximately 0.1% of all hospital admissions due to acute abdominal pain. This condition develops when the blood supply to the intestinal tract is compromised. AMEI is classified into three main types: arterial occlusion (either embolic or thrombotic), venous thrombosis, and low-flow (non-occlusive) ischemia related to hypoperfusion [1, 2, 3]. Arterial occlusion, most commonly embolic, accounts for approximately 50% of cases, frequently affecting the superior mesenteric artery. Mesenteric venous thrombosis is linked to hypercoagulable states and carries a lower mortality rate, around 20–40%. Low-flow (non-occlusive) ischemia, associated with systemic hypoperfusion such as cardiogenic shock or sepsis, can result in mortality rates exceeding 70% [4]. The clinical presentation is often nonspecific. This makes early diagnosis challenging and often leads to delays, irreversible complications such as bowel necrosis occur. Early symptoms include sudden, severe abdominal pain, often out of proportion to physical exam findings. Nausea, vomiting, diarrhea, or hematochezia may occur. In later stages, signs of peritonitis and shock develop, indicating bowel necrosis [5]. Early recognition is crucial, as intervention within the first 6–12 hours can prevent progression to necrosis. Therefore, an integrated approach combining advanced imaging and laboratory markers is critical [3].

## Imaging Methods for Early Diagnosis

*Multidetector computed tomography angiography* (CTA) is gold standard in suspected AMEI. Its sensitivity ranges from 93% to 100%, and specificity from 95% to 100% . It allows visualization of arterial thrombosis, embolism, stenosis, venous thrombosis, ischemic bowel wall changes, and portal venous gas. CTA is particularly vital for detecting pneumatosis (gas in the bowel wall), present in about 20% of late-stage cases, and can identify specific arterial or venous filling defects in over 85% of early AMEI cases, aiding timely diagnosis [6, 7].

*Invasive angiography* remains the gold standard for direct visualization of vascular abnormalities and offers the advantage of simultaneous therapeutic intervention. However, it is primarily reserved for therapeutic procedures [8].

The integration of CTA and angiographic imaging provides comprehensive evaluation of the gastrointestinal tract, facilitating early diagnosis and subsequent management. High clinical suspicion, coupled with knowledge of imaging findings, is essential for accurate diagnosis and improved patient outcomes. CTA stands as a cornerstone in the diagnostic workup of suspected AMEI, offering precise and reliable results. Recent studies emphasize the accuracy of CTA in assessing bowel and mesenteric changes, thereby reinforcing their critical role in clinical decision-making. CTA can directly identify the cause of ischemia by detecting arterial or venous filling defects (thrombi or emboli) in the superior mesenteric

artery (SMA) or superior mesenteric vein (SMV). It can also reveal arterial narrowing or vasospasm characteristic of non-occlusive mesenteric ischemia (NOMI). Importantly, vascular findings often manifest before irreversible intestinal tissue damage. Early CT signs include:

- Abnormal Bowel Wall Enhancement. This is a key indicator. Reduced or absent enhancement suggests poor perfusion (pale ischemia), while hyperenhancement might indicate vascular congestion or reperfusion injury.

- Venous Dilation: This is another early and sensitive sign of ischemia, detectable as early as one hour after arterial occlusion.

CTA provides detailed anatomical information, helping to determine the extent of the affected bowel, differentiate between reversible ischemia and irreversible transmural necrosis, and identify associated conditions like free air (pneumoperitoneum) or solid organ infarcts. CTA can also rule out other common causes of acute abdominal pain (e.g., bowel obstruction, perforation, aortic dissection), thus preventing diagnostic delays. The detailed CTA images guide the therapeutic strategy, whether it involves endovascular revascularization, surgical bowel resection, or medical management. CTA modalities are fast, safe, and non-invasive, making them the preferred techniques in the evaluation of AMEI. Their utility in early diagnosis and timely intervention plays a significant role in reducing the high morbidity and mortality associated with this condition. While historically the "gold standard" for diagnosis, conventional angiography is now primarily used as a therapeutic tool. It allows simultaneous diagnosis and minimally invasive interventions such as targeted vasodilator infusion for NOMI or thrombolysis for occlusions [9].

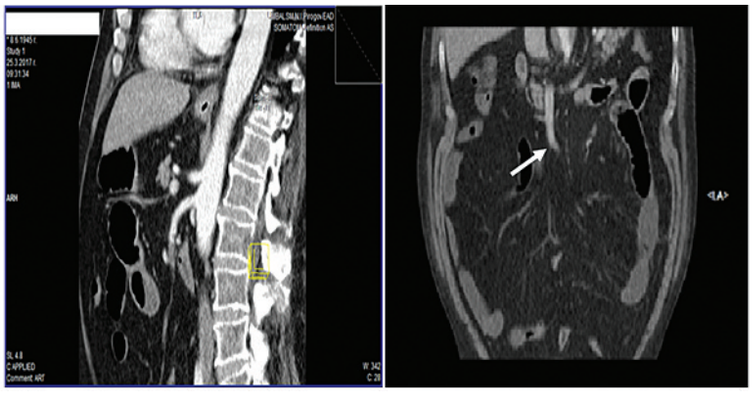

**Figure 1.** ***CT angiography of the aorta:*** *from the level of T10 to the level of L5 along the right-dorsal contour, a filling defect with a width of up to 14 mm is detected – non-enhancing in the arterial phase [8].*

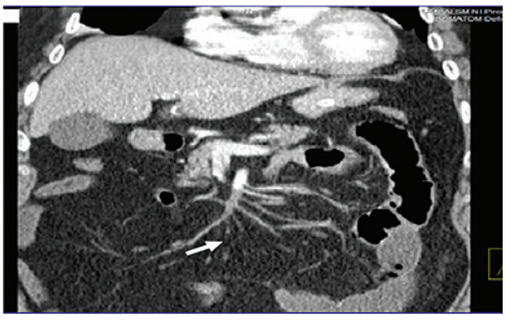

**Figure 2.** ***Abdominal CTA:*** *It is observed that the distal branches to the dilated bowel loops of the SMA are less opacified in the arterial phase [8].*

For the assessment of mesenteric blood flow, a scale analogous to the TIMI (Thrombolysis in Myocardial Infarction) scale used for coronary blood flow can be utilized [10]. The classification is as follows:

- Type 0 (TIMI 0 Flow): Complete absence of angiographic evidence of blood flow within the Superior Mesenteric Artery (SMA).
- Type 1 (TIMI 1 Flow): Angiographic evidence of minimal perfusion immediately up to the origin of the middle colic artery, with no or very limited distal filling of the arterial branches.
- Type 2 (TIMI 2 Flow): Angiographic evidence of perfusion extending to the ileocolic artery, past the initial point of obstruction, characterized by limited distal branch filling and minimal or sluggish distal perfusion.
- Type 3 (TIMI 3 Flow): Angiographic evidence of optimal perfusion with complete and rapid filling of all distal branches.

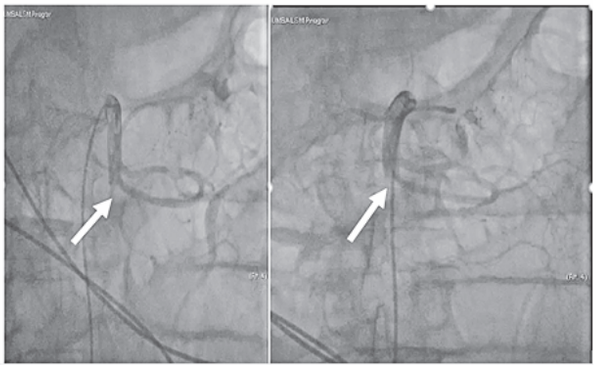

**Figure 3.** ***Selective Angiography of the SMA:*** *Acute occlusion of the vessel is visualized immediately distal to the middle colic artery - a typical anatomical location, with Type 0 blood flow [10].*

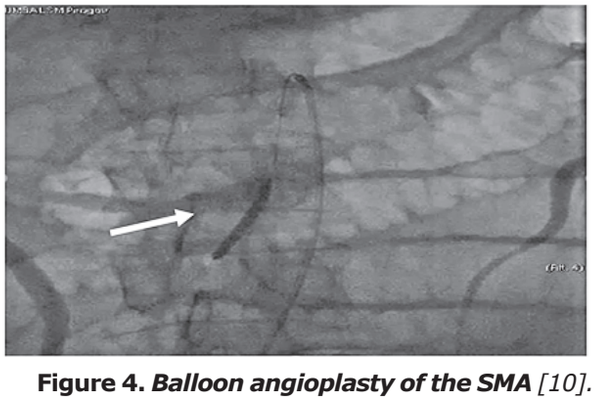

**Figure 4.** ***Balloon angioplasty of the SMA*** *[10].*

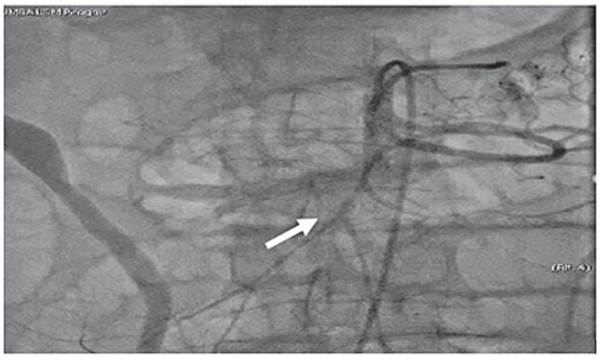

**Figure 5.** ***Partial recanalization of the SMA (massive thromboembolic burden), Type 2 blood flow*** *[10].*

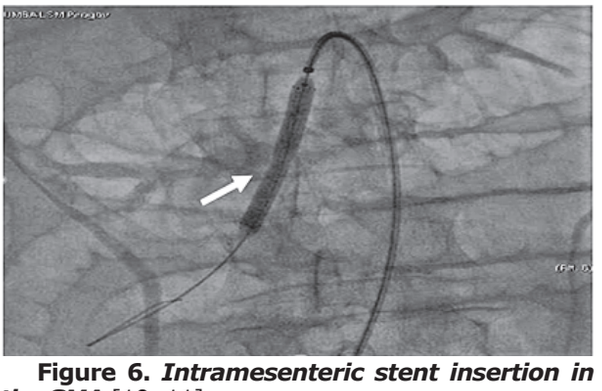

**Figure 6.** ***Intramesenteric stent insertion in the SMA*** [10, 11].

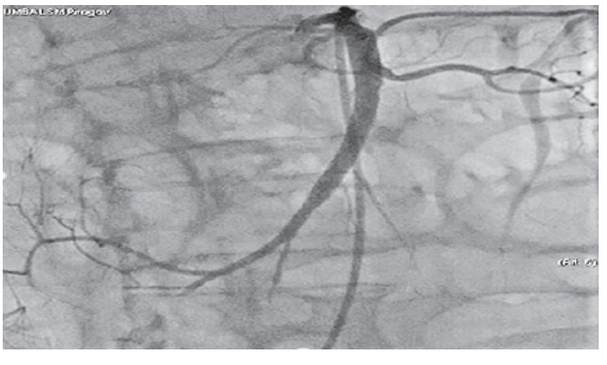

**Figure 7.** ***Achieved complete perfusion of the SMA, final Type 3 blood flow*** **[11].**

*Duplex ultrasound* has a sensitivity of approximately 70–80% and is especially useful for patients with contraindications to contrast or in unstable conditions, though it remains operator-dependent [12].

*Magnetic resonance angiography* (MRA) has similar sensitivity to CTA but is less frequently used due to longer scan duration [12].

**Laboratory Parameters**

Laboratory parameters play a crucial role in the early diagnosis of acute mesenteric ischemia [13].

*Elevated serum lactate* is one of the most important indicators. Levels above 2.0 mmol/L have a sensitivity exceeding 90% for detecting AMEI. In advanced stages, lactate levels often surpass 4.0–5.0 mmol/L, correlating with bowel necrosis and worse prognosis.

*White blood cell (WBC) count* greater than 15,000/μL is commonly observed in AMEI. Sensitivity for leukocytosis in AMEI is around 80%, although specificity is lower since elevated WBC can occur in other abdominal conditions as well.

*D-Dimer* levels above 1500 ng/mL show high sensitivity (>95%) for AMEI. However, specificity is limited, as elevated D-Dimer can be present in other thrombotic or inflammatory conditions.

*C-Reactive Protein* (CRP) levels above 100 mg/L are associated with more advanced stages of AMEI, particularly with bowel necrosis. In early stages, CRP may remain within normal limits.

*Elevated Creatine Kinase levels,* particularly above 1000 U/L, are indicative of bowel wall necrosis and advanced ischemia.

*Amylase and lipase levels* may show moderate elevation, typically 1.5 to 2 times the upper normal limit, but these are non-specific markers and must be interpreted with caution.

*Metabolic acidosis* with a pH below 7.3 and a base deficit greater than −6 is indicative of tissue hypoperfusion and is a critical laboratory finding in AMEI [14].

Regarding laboratory data, in addition to lactate and D-dimer, attention should be paid to metabolic acidosis [15]. Elevated white blood cell counts further support the diagnosis, particularly in combination with elevated creatine kinase, which serves as a marker of advanced bowel necrosis. These laboratory parameters, in conjunction with clinical evaluation and imaging studies, significantly enhance the early detection and management of AMEI, ultimately improving patient outcomes [16].

**Conclusion**

AMEI remains a challenge in emergency medicine. Early diagnosis, an integrated approach with imaging and laboratory methods, and multidisciplinary collaboration are key to improving outcomes. The condition requires a high index of clinical suspicion due to nonspecific symptoms and rapid progression. Modern imaging modalities, such as CTA, and targeted use of laboratory markers play a crucial role.

The multidisciplinary approach involving abdominal surgeons, interventional radiologists, and intensivists enhances coordination and reduces time to intervention.

Despite high mortality, advancements in diagnosis and therapy in recent years provide grounds for optimism. Increasing clinician awareness and understanding of risk factors can lead to earlier recognition and, consequently, better patient outcomes.

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# Основни акценти от актуализираните препоръки на световната асоциация по спешна хирургия при остра мезентериална исхемия

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# Key highlights from the updated world society of emergency surgery guidelines on acute mesenteric ischemia

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**РЕЗЮМЕ:**

Острата мезентериална исхемия е сериозно медицинско състояние, което изисква бърза интервенция за предотвратяване на некроза и висока смъртност. Последните препоръки на Световната асоциация по спешна хирургия наблягат на бързата диагностика и минимално инвазивните процедури. Те също така очертават хирургически стратегии, вариращи от емболектомия до резекция на некротични сегменти и подчертават значението на мултидисциплинарния подход и периоперативното поведение, включително интензивно наблюдение и антикоагулация. Тези насоки целят да намалят смъртността и усложненията, като предоставят на клиницистите ясни, основани на доказателства инструменти за ефективно поведение.

**Ключови думи:** остра мезентериална исхемия, мезентериална тромбоза и емболия, препоръки.

**ABSTRACT:**

Acute mesenteric ischemia is a serious medical condition that requires prompt intervention to prevent necrosis and high mortality. Recent guidelines from the World Society of Emergency Surgery emphasize rapid diagnosis and minimally invasive procedures. They also outline surgical strategies ranging from embolectomy to resection of necrotic segments and highlight the importance of a multidisciplinary approach and perioperative management, including intensive monitoring and anticoagulation. These guidelines aim to reduce mortality and complications by providing clinicians with clear, evidence-based tools for effective management

**Key words:** acute mesenteric ischemia, mesenteric thrombosis and embolism, guidelines.

## Introduction

Acute mesenteric ischemia (AMI) is a serious and life-threatening condition requiring prompt and accurate diagnosis. The incidence of AMI, particularly in elderly patients with atherosclerosis, presents significant diagnostic challenges. Delayed treatment often results in high mortality rates. Clinical symptoms can be non-specific, underscoring the need for a high index of clinical suspicion and effective diagnostic algorithms [1]. AMI may be occlusive or non-occlusive (NOMI), with the primary etiology defined as mesenteric arterial embolism (50%), mesenteric arterial thrombosis (15–25%), or mesenteric venous thrombosis (5–15%) [2,3]. The prevalence of AMI has changed in recent decades. The acute mesenteric occlusion among patients with an acute abdomen may vary from 17.7% in emergency laparotomy and 31.0% in laparotomy for elderly non-trauma patients [4]. Mesenteric arterial embolism decreased to 25% of cases [3, 5]. Mesenteric arterial thrombosis was the second most common cause of mesenteric ischemia, which historically accounted for 20–35% and recently increased to 40% [5].

In recent years, advances in imaging techniques and minimally invasive interventions have significantly improved the early detection and treatment of AMI. In this context, the updated guidelines from the World Society of Emergency Surgery represent a major step forward in standardizing the diagnostic and therapeutic approach. The aim of this review is to present the key highlights of the recommendations, providing clinicians with a practical guide to optimize the management of acute mesenteric ischemia patients and improve patient outcomes.

## Risk factors

The etiology of AMI has changed over the years with increasing percentages of acute arterial thrombosis due to atherosclerosis which may in part be explained by modern anticoagulant therapy used for the treatment of atrial fibrillation. Although the mechanism is still unknown, heart failure, renal failure, cardiac surgery using cardiopulmonary bypass, and the use of catecholamine are reported as risk factors for AMI [6].

The incidence of AMI increases exponentially with age. In patients aged 75 years or older, AMI is a more prevalent cause of acute abdomen than appendicitis [7]. The incidence of AMI in an 80-year-old is roughly tenfold that of a 60-year-old patient [8].

Abdominal compartment syndrome with very high intraabdominal pressure may cause bowel ischemia that is complicated with ischemia–reperfusion injury when decompression laparotomy is performed [9].

AMI has been described in patients with coronavirus disease (COVID -19), probably related to large vessel thromboembolic events as well as to small vessel thrombosis linked to hypercoagulability and fibrinolysis shutdown [10].

NOMI represents a cause of secondary worsening in septic shock, particularly in septic patients treated with high-dose vasoactive drugs. Clinical scenario and risk factors differentiate AMI as mesenteric arterial emboli, mesenteric arterial thrombosis, non-occlusive mesenteric ischemia (NOMI), or mesenteric venous thrombosis (Weak recommendation based on low-quality evidence 1C) [1].

## Diagnostics

Delay in diagnosis is the dominant factor that accounts for high mortality rates of 30–70% despite increased knowledge of this entity [11, 12]. Every 6 h of delay in diagnosis doubles mortality [13]. The updated guidelines emphasize the critical importance of early and precise diagnosis of AMI. The clinical scenario of a patient complaining of excruciating abdominal pain with an unrevealing abdominal examination is classic for early AMI [14]. Severe abdominal pain out of proportion to physical examination findings should be assumed to be AMI until disproven. (Strong recommendation based on low-quality evidence 1C) [1]. Patients often have a history of chronic postprandial abdominal pain, progressive weight loss, and previous revascularization procedures for mesenteric arterial occlusion. Patients with NOMI have pain that is generally more diffuse and episodic associated with poor cardiac performance. These patients are more likely to have suffered from cardiac failure, and recent surgery. Several other

smaller cohorts also reported hemodialysis as a risk factor of NOMI [15, 16]. Unexplained abdominal distension or gastrointestinal bleeding may be the only signs of acute intestinal ischemia in NOMI and may be undetectable in sedated patients in approximately 25% of cases [17, 18]. NOMI should be suspected of critically ill patients with abdominal pain or distension requiring vasopressor support and evidence of multiorgan dysfunction (Weak recommendation based on low-quality evidence 2C) [1].

Clinical examination and routine laboratory tests are of only little value in reaching an early and reliable diagnosis of NOMI. A radiograph is usually the initial test in patients with acute abdominal pain, but it has a limited role in the diagnosis of mesenteric ischemia, especially in the early setting. A negative radiograph does not exclude mesenteric ischemia [19]. Plain X-ray is not recommended in evaluating patients for intestinal ischemia (Strong recommendation based on moderate-quality evidence 1B) [1].

The gold standard for diagnosis is computed tomography angiography (CTA). The recommendations emphasize that in suspected cases, CTA should be performed to assess for thrombosis, embolism, or stenosis of the mesenteric vessels [20]. Volume rendering is now a semiautomatic workflow component of many CT machines. These can help remote communities with less experienced staff. CTA should be performed without delay in any patient with suspicion for AMI. (Strong recommendation based on high-quality evidence 1A). CTA is conducted with contrast enhancement and in a phase that optimally visualizes the arterial system. This allows early detection of ischemia before irreversible changes occur. In cases where CTA is not feasible or contrast is contraindicated, magnetic resonance angiography (MRA) may be considered, though with lower sensitivity [1].

Doppler sonography is recommended as a screening tool in high-risk patients but cannot replace CTA in the acute phase. Further careful interpretation of imaging findings is advised—absence of pneumatosis or portal venous gas does not exclude early acute mesenteric ischemia. Accurate assessment of perfusion and detection of thrombosis are critical for timely therapeutic decisions. Expanding the scope, recent developments in imaging modalities, such as CTA and Doppler ultrasound, have enhanced the ability to detect vascular abnormalities swiftly. Moreover, novel endovascular techniques offer less invasive options for revascularization, reducing procedural risks [21].

Although laboratory results are not definitive, they may help to corroborate clinical suspicion. More than 90% of patients will have an abnormally elevated leukocyte count [22]. The second most encountered abnormal finding is metabolic acidosis with elevated lactate level, which occurs in 88% [23]. Serum lactate levels are emphasized as a supplementary biochemical marker of tissue hypoperfusion. There are no laboratory parameters that are sufficiently accurate to conclusively identify the presence or absence of ischemic or necrotic bowel, although elevated l-lactate, leukocytosis, and D-dimer may assist (Weak recommendation based on moderate-quality evidence 2B) [1].

Diagnostic laparoscopy is feasible as a bedside procedure in the intensive care unit with the advantage of avoiding time delay for awaiting operating room availability and preventing adverse events during critically ill patients transfer. However, the routine use of diagnostic laparoscopy in AMI has not been generally adopted [24]. Prompt laparoscopy/laparotomy should be done for patients with overt peritonitis (Strong recommendation based on low-quality evidence 1C) [1].

The integration of these advanced tools into clinical practice is crucial for improving diagnostic accuracy and therapeutic efficacy. By adopting these comprehensive guidelines, healthcare providers can ensure timely and precise intervention, minimizing the progression of ischemia and associated complications. Thus, the updated recommendations serve as a cornerstone for enhancing patient care, promoting multidisciplinary collaboration, and ultimately improving survival rates and quality of life for affected individuals [1,25].

**Therapeutic Approaches**

In endovascular thrombolytic therapy, the current recommendations specify the use of tissue plasminogen activator in low doses, with a prolonged local infusion over 12 to 24 hours, depending on the clinical response. For mechanical thrombectomy, thrombectomy catheters with aspiration mechanisms are often recommended, especially for proximal thrombi [26].

The guidelines recommend self-expanding stents with high radial force, particularly for high-risk anatomical locations. The intervention time windows are defined—ideally within 6 hours from symptom onset, although in certain patients with slow progression, this window may be extended [26].

The surgical approach is recommended for patients with perforation, diffuse peritonitis, or extensive bowel necrosis. Special attention is given to patients in hemodynamic instability—immediate surgery is advised, combined with intraoperative angiography if feasible [26].

Fluid resuscitation with crystalloid and blood products is essential for the management of the patient with suspected AMI [27]. When the diagnosis of AMI is made, fluid resuscitation should commence immediately to enhance visceral perfusion. Electrolyte abnormalities should be corrected, and nasogastric decompression initiated (Strong recommendation based on moderate-quality evidence 1B) [1].

The high risk of infection among patients with AMI outweighs the risks of acquired antibiotic resistance, and therefore, broad-spectrum antibiotics should be administered early during treatment (Strong recommendation based on low-quality evidence 1C) [1,28].

Endovascular techniques have become popular in revascularization of the superior mesenteric artery (SMA). No randomized control trial has been performed to assess and compare open surgery to an endovascular approach, as patients with AMI are very heterogenic and physiologically different [29]. Endovascular revascularization procedures are the primary option in cases of arterial occlusion when sufficient expertise is available (Strong recommendation based on low-quality evidence 1C) [1]. The damage control laparotomy strategy (abbreviated laparotomy) has been an accepted technique in trauma care for the past 30 years. It is an important option for patients with AMI [30]. Damage control surgery with temporary abdominal closure is an important adjunct for patients who require intestinal resection allowing reassessment of bowel viability and in situations of severe abdominal sepsis (Strong recommendation based on low-quality evidence 1B) [1].

The first line treatment for mesenteric venous thrombosis is anticoagulation. Systemic thrombolytic therapy is rarely indicated. When clinical signs demand operative intervention, one should resect only obviously necrotic bowel utilizing damage control techniques since anticoagulation therapy may improve the clinical picture over the ensuing 24–48 h. Early use of heparin has been associated with improved survival [31]. Mesenteric venous thrombosis can often be successfully treated with a continuous infusion of unfractionated heparin (Strong recommendation based on moderate-quality evidence 1B) [1]. Most patients treated for AMI require lifelong anticoagulant/antiplatelet therapy to prevent relapse. In patients following endovascular stent placement, clopidogrel is administered for 6 months and acetylsalicylic acid as lifelong maintenance treatment. However, there is no scientific data on dual antiplatelet therapy after SMA stenting and the recommendation is based on experience from coronary interventions. When recovered following acute illness, most patients can switch to direct oral anticoagulants or vitamin K antagonists. Anticoagulation is given for 6 months, but most patients with underlying hypercoagulability should be considered for lifelong anticoagulation [32]. Patients undergoing revascularization should have surveillance imaging and long-term anticoagulation (Strong recommendation based on moderate-quality evidence 1B) [1].

The central principle of NOMI management is the treatment of the underlying precipitating cause. Fluid resuscitation, optimization of cardiac output, and elimination of vasopressors remain important primary measures. Additional treatment may include systemic

anticoagulation (heparin) and the use of catheter-directed infusion of vasodilatory and antispasmodic agents, most commonly papaverine hydrochloride [33]. When NOMI is suspected, the focus is to correct the underlying cause and improve mesenteric perfusion. Infarcted bowels should be resected promptly (Strong recommendation based on low-quality evidence 1C) [1].

Depending on cardiac output and peripheral vascular resistance, a combination of noradrenaline and dobutamine rather than vasopressin should be considered to minimize the possible negative impact on the intestinal microcirculation [34].

Postoperative intensive care of AMI patients is directed toward improved intestinal perfusion and the prevention of multiple organ failure (Strong recommendation based on low-quality evidence 1C) [1]. Recent published evidence suggests that treatment of occlusive AMI in "intestine stroke centers" using a multidisciplinary approach improves outcomes [35, 36]. The goal of multidisciplinary approach is to keep the time to reperfusion as short as possible. The team often includes general surgeon (preferably an emergency surgery specialist), vascular surgeon, interventional radiologist, and intensivist. The concept of "intestinal stroke centers" has been promulgated in France and in China [37, 38]. Treatment of AMI is optimal in a dedicated center using a focused care bundle and a multidisciplinary team (Strong recommendation based on low-quality evidence 1C) [1].

The loss of large amounts of small bowels due to AMI can result in short bowel syndrome (SBS) and intestinal failure. SBS is associated with poor quality of life and morbidity, which increases with age and comorbidities [39]. Management of patients with SBS can be challenging, especially in case of ostomies with associated large fluid losses and electrolyte imbalances [40]. Patients with short bowel syndrome following extensive bowel resection should have restoration of digestive continuity in association with hormonal therapy to optimize absorptive function and achieve nutritional autonomy (Weak recommendation, low-quality evidence 1C) [1]. Surgery may not be the best solution, especially in elderly frail patients unable to tolerate long-term parenteral nutrition. In this regard, a preoperative discussion with the patient and their family is essential in guiding clinical decisions [41]. In case of massive gut necrosis, a careful assessment of the patient's underlying comorbidities and advanced directives is advisable to determine the optimal therapeutic strategy, which could include palliation (Weak recommendation, low-quality evidence 1C) [1].

**Clinical Examples**

According to the updated recommendations, let us illustrate specific clinical cases. For instance, in a patient presenting with acute abdominal pain, elevated serum lactate levels, and inconclusive ultrasound findings, immediate CTA reveals a thrombus in the superior mesenteric artery. In this scenario, the guidelines recommend urgent endovascular interventions such as thrombolysis or thrombectomy [1,21].

Another example: in a patient with a subacute form, where CTA demonstrates stenosis of the mesenteric vessel, elective stenting is advised. For patients with already developed bowel necrosis, the recommendation is a combined approach—emergency laparotomy with resection of the necrotic bowel segment followed by revascularization [26].

**Conclusion**

The updated recommendations of the World Society of Emergency Surgery for AMI not only unify the approach to this critical condition but also open new perspectives for improving long-term outcomes. Early diagnosis based on modern imaging modalities, such as CTA and Doppler ultrasound, and minimally invasive endovascular techniques have already demonstrated significant reductions in mortality. The integration of these advanced tools into clinical practice is crucial for improving diagnostic accuracy and therapeutic efficacy. Moreover, novel endovascular techniques offer less invasive options for revascularization, reducing procedural risks. In addition, a personalized approach to patients—considering the severity of ischemia, the presence of comorbidities, and the time to diagnosis—

plays a pivotal role in tailoring treatment strategies to individual patient needs. This integration of contemporary science, clinical experience, and a multidisciplinary approach equips the medical community with a robust toolkit aimed at improving survival rates and enhancing quality of life for patients suffering from this severe pathology. By fostering collaboration among various specialties and leveraging state-of-the-art technology, the healthcare system becomes better positioned to address AMI with precision and confidence.

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# Герминативно клетъчен карцином и ролята на високодозовата химиотерапия и тандемна автоложна трансплнтация на стволови клетки при рецидивирало/рефрактерно заболяване

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# Germ Cell Tumor and the Role of High-Dose Chemotherapy and Tandem Autologous Stem Cell Transplantation for Relapsed/Refractory Disease

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**РЕЗЮМЕ:**

Герминативноклетъчните тумори (ГКТ) са най-честите солидни злокачествени заболявания при млади мъже, които се отличават с висока чувствителност към платина-базирана терапия. Въпреки високия процент на излекуване, случаите с рецидивиращ или рефрактерно ход представляват сериозно терапевтично предизвикателство. Настоящият обзор поставя акцент върху ролята на високодозовата химиотерапия (ВДХТ), подкрепена от тандемна автоложна трансплантация на стволови клетки (АСКТ), като критична стратегия за преодоляване на лекарствената резистент. Предстоящите резултатите от проучването TIGER, ще бъдат от решаващо значение за определяне на необходимостта от по-нататъшна интензификация (три или повече цикъла) или настоящият тандемен подход продължава да предлага оптималния баланс между ефикасност и безопасност.

**ABSTRACT:**

Germ cell tumors (GCTs) are the most common solid malignancies in young men, distinguished by their high sensitivity to platinum-based therapy. Despite high cure rates, cases with a relapsed or refractory course present a significant therapeutic challenge. This review highlights the role of high-dose chemotherapy (HDCT) supported by tandem autologous stem cell transplantation (ASCT) as a critical strategy for overcoming drug resistance. The upcoming results of the TIGER trial will be crucial in determining whether further intensification (three or more cycles) is necessary, or whether the current tandem approach continues to offer the optimal balance between efficacy and safety

**Ключови думи:** Герминативноклетъчни тумори, високодозова химиотерапия, тандемна трансплантация, рецидив, клинични проучвания

**Keywords:** Germ cell tumors, high-dose chemotherapy, tandem transplantation, ASCT, relapse, clinical trials

## Introduction

GCTs represent a heterogeneous group of neoplasms originating from primary germ cells. Although gonadal tumors (testes, ovaries) are the most common, GCTs can also arise in extragonadal sites, including the mediastinum, retroperitoneum, or the sacrococcygeal region. GCT is a relatively rare oncological disease in the general population, accounting for about 1-2% of all malignant neoplasms in men. Its epidemiological significance stems from the fact that it is the most common solid tumor in young men (in the age group of 15–45 years) [1].

## Classification and Risk Factors

The histological classification divides GCTs into two main groups with distinct clinico-pathological characteristics:

• Seminomas: Characterized by a later peak incidence (around 35–39 years), a more indolent biological behavior, and high radio- and chemosensitivity.

• Non-Seminomatous Germ Cell Tumors (NSGCT): Typically more aggressive, with an earlier peak incidence (around 25–29 years).

The most significant risk factor for the development of GCT is cryptorchidism (undescended testicle), which significantly increases the risk of developing cancer, even after surgical correction in childhood. Other important risks include a personal history of cancer in the opposite testicle and the presence of Germ Cell Neoplasia In Situ (GCNIS), which is a direct precursor to invasive cancer. The risk is also elevated with a family history (especially in a brother), certain congenital anomalies (Klinefelter syndrome), and infertility [2].

Determining the serum levels of tumor markers is mandatory for staging, risk stratification, and monitoring the therapeutic response. The main markers are: Alpha-fetoprotein (AFP); Human Chorionic Gonadotropin (HCG); Lactate Dehydrogenase (LDH)

## Prognostic Systems

The internationally recognized prognostic system IGCCCG (International Germ Cell Cancer Collaborative Group) is used for the treatment of metastatic disease (Stage II and III), which divides patients into prognostic groups [3, 4]:

1. Prognostic Groups for Seminoma

• Good Prognosis: Metastases limited to the lung and/or lymph nodes, regardless of HCG and LDH levels.

• Intermediate Prognosis: Presence of visceral metastases (excluding the lung), but without CNS metastases.

2. Prognostic Groups for Non-Seminoma

The classification is based on the location of metastases and marker levels:

• Good Prognosis: Limited spread (lymph nodes/lung) and low marker levels (AFP<1000, HCG<5000).

• Intermediate Prognosis: Limited spread, but with marker levels elevated above the thresholds for good prognosis.

• Poor Prognosis: Defined by the presence of visceral metastases (liver or CNS) or extremely high marker levels (AFP>10,000 or HCG>50,000 OR LDH>10 times ULN).

## Treatment and Prognosis

The treatment of GCTs is exceptionally successful : the cure rate in early stages often exceeds 95%, and even in metastatic forms, it reaches 80–90%.Radical inguinal orchiectomy is the first mandatory step in the treatment of the primary tumor, serving simultaneously for diagnosis and therapy. Testicular biopsy is avoided to prevent the risk of spreading tumor cells. After the operation, the subsequent treatment depends on the histological variant of the tumor and its stage with [5,6]:

1. Treatment of Seminomas

For early stage (I), the most common approach is active surveillance. Alternatively,

adjuvant chemotherapy, usually a single course with Carboplatin, can be administered to reduce the risk of relapse. For advanced stage (II and III), the main method is Platinum-based chemotherapy, most often administered through the BEP regimen (Bleomycin, Etoposide, Platinum).Radiotherapy is used less frequently today, but can be effective for certain cases in stage II.

2. Treatment of Non-Seminomas

For early stage (I), active surveillance may be chosen for low-risk tumors.For higher risk, doctors may recommend adjuvant chemotherapy (one to two BEP courses) or Retroperitoneal Lymph Node Dissection (RPLND) – surgical removal of abdominal lymph nodes.For advanced stage (II and III), treatment includes chemotherapy (3-4 courses of BEP or similar regimens). If residual tumor masses remain after chemotherapy, they must be removed via an additional operation (often RPLND) to check if they contain viable tumor, necrosis, or benign teratoma.

3. Treatment of Relapsed/Refractory Disease

The approach for treating refractory or relapsed Germ Cell Tumor (GCT) is complex and requires intensive therapy. The goal of treatment is salvage chemotherapy, followed by consolidation, often with high-dose chemotherapy. For patients with relapse after standard first-line chemotherapy (e.g., BEP, VIP), the standard approach is second-line chemotherapy based on Cisplatin, but with different combinations: VIP (Vepezid/Etoposide, Ifosfamide, Cisplatin) ; TIP (Paclitaxel, Ifosfamide, Cisplatin) ; VeIP (Vepezid/Etoposide, Ifosfamide, Cisplatin) ; ICE (Ifosfamide, Carboplatin, Etoposide)[7].

For patients who achieve a response (complete or partial) to second-line chemotherapy, high-dose HDCT with autologous stem cell transplantation is recommended as consolidation treatment. The goal is to improve long-term survival, especially in patients with a good prognosis for salvage treatment. HDCT regimens usually include high doses of Carboplatin and Etoposide, often administered in two sequential cycles. It has been established as a life-saving intervention since since the early 1990s [8].

**Autologous Stem Cell Transplantation as the Standard Salvage Therapy for Relapsed GCTs**

The primary rationale for utilizing HDCT in solid tumors is the potential to overcome chemoresistance through dose escalation. Unlike hematological malignancies, treatment-related mortality (TRM) is minimized (approx. 1%) and ASCT serves as a "rescue" for hematopoiesis following myeloablative doses. GCTs serve as a successful model for the application of HD-ASCT.

The comparative analysis of HDCT regimens reveals a critical evolution in the management of R/R GCTs. Data from major clinical series, presented in Table 1, including the Indiana University experience [10], the Alberta study [14], and the EBMT registry, establish the benefit of ASCT following HDCT, confirming it as the standard salvage therapy for high-risk patients after initial treatment failure. Success is highest when this intervention is applied early as a second-line (first salvage) therapy, providing significant potential for long-term progression-free survival (PFS) and overall survival (OS). The primary clinical debate in the field currently is on the choice of regimen—specifically whether to utilize a tandem or triplet approach. While triplet regimens, such as the TI-CE protocol, strive for maximum dose intensity through three consecutive cycles, they are frequently associated with higher cumulative toxicity and a potential treatment-related mortality (TRM) of up to 3%.

In contrast, the tandem approach involves two sequential cycles of HDCT, each followed by transplantation, and has been associated with improved 3-year PFS and OS according to large retrospective analyses. This tandem strategy demonstrates a manageable intensity profile with a robust therapeutic effect and exceptionally low treatment-related mortality, making it a safer alternative for patients who may not tolerate the highest levels of toxic aggression. The clinical efficacy of these interventions is further highlighted by the stabilization of PFS after the two-year mark. When a two-year PFS remains constant through to the five-year mark, it indicates a "plateau effect"

suggesting that patients who surpass this clinical milestone without relapse are likely cured. Currently, the oncology community is awaiting the results of the TIGER trial [15], a randomized phase III study comparing conventional-dose TIP chemotherapy with the triplet TI-CE regimen. These results will be pivotal in determining whether the added intensity of a third cycle offers a significant survival advantage over the established tandem strategy.

Within this therapeutic framework, nonseminomatous germ cell tumors (NSGCT) require specific clinical considerations due to their aggressive nature and propensity for visceral and brain metastases. NSGCT patients often fall into the "poor prognosis" category of the IGCCCG classification due to non-pulmonary visceral spread or significantly elevated tumor markers, such as AFP exceeding 10,000 ng/mL or hCG over 50,000 IU/L [15]. For these individuals, HDCT is not merely an option but a vital necessity for survival upon the first relapse. During treatment, the dynamics of these markers serve as critical prognostic indicators; a rapid decline in AFP and hCG levels following the first tandem cycle is a strong positive predictor of a complete response.

The selection of specific pharmacological agents further optimizes outcomes for NSGCT, particularly when involving regimens that include Thiotepa [16]. The inclusion of Thiotepa is advantageous due to its excellent penetration of the blood-brain barrier, making it a superior choice for non-seminoma patients with a high risk of central nervous system involvement. Furthermore, this intensified approach addresses the challenges posed by extragonadal primaries, such as primary mediastinal non-seminoma germ cell tumors (PMNSGCT) [17]. While these cases historically carry a poorer prognosis, early intensification with tandem HDCT and ASCT has been shown to significantly improve survival outcomes compared to conventional-dose chemotherapy, establishing it as the preferred strategy for managing this challenging and aggressive subgroup.

**Table 1.** *Review of Key Clinical Studies (HDCT/ASCT for R/R GCT), [10-14]*

| Study Name / Analysis | Number of Patients (n) | Indication | Compared Therapeutic Interventions | Results (OS / PFS) | Conclusion |
|---|---|---|---|---|---|
| CIBMTR/EBMT Analysis (2019) | 2395 | Relapsed/Refractory male GCT | Single Transplantation (ST) versus Tandem Transplantation (TT) | 3-year PFS: Increased to 47% (2010-15). 3-year OS: Increased to 54% (2010-15). TT is associated with better results. | Results have significantly improved over time, associated with the increased use of Tandem Transplants and the earlier administration of ASCT. |
| Indiana University (Retrospective Analysis, 2017) | 364 | Relapsed/Metastatic GCT (2nd line or later) | HDC + PBSCT (High-Dose Chemotherapy with ASCT) | 2-year PFS: 63% (2nd line); 49% (3rd+ line). 2-year OS: 66%. | HDC + PBSCT is a curative option for relapsed metastatic GCT, even in late lines of treatment, but outcomes are better when applied earlier. |
| EBMT PMNSGCT Report (2024) | 69 | Primary Mediastinal Non-Seminoma GCT (PMNSGCT) | HDC + ASCT (mainly Carboplatin/Etoposide) | 5-year PFS: 51.8% (applied as first line); 26.8% (applied for subsequent relapses). | HDC with ASCT can be a therapeutic option for PMNSGCT after first relapse or as part of a first-line therapy program for very high risk. |
| International Multicenter Analysis (Seftel et al., 2011) | 71 | Relapse or incomplete response to first-line CT | Single ASCT | 5-year OS: 44.7%. 5-year EFS (Event-Free Survival): 43.5%. | ASCT leads to successful long-term outcomes for a large subgroup of patients with high-risk GCT. Late relapses are also observed. |

| | | | | | |
|---|---|---|---|---|---|
| Multicenter Analysis (e.g., from Alberta Experience, citing a larger series) | 1594 | Relapsed mGCT | HDC-ASCT versus Conventional Dose Chemotherapy (CDC) | 2-year PFS: 50% (HDC-ASCT) versus 28% (CDC). 5-year OS: 53% (HDC-ASCT) versus 41% (CDC). | Results favor high-dose chemotherapy with ASCT as salvage therapy, especially compared to conventional chemotherapy. |
| Turkish Single-Center Study (Yıldız et al., 2020) | 30 | Relapsed/Refractory Extragonadal GCT (EGGCT) | ASCT as 2nd or 3rd salvage therapy (after TIP/VIP) | Non-specific data for PFS/OS, but significantly increased survival is noted with multimodal treatment and ASCT. | ASCT is an option for salvage treatment in extragonadal GCT, despite their worse prognosis compared to gonadal GCTs. |

**Legend: ASCT:** Autologous Stem Cell Transplantation; **CIBMTR:** Center for International Blood and Marrow Transplant Research; **CDC:** Conventional Dose Chemotherapy; **EBMT:** European Society for Blood and Marrow Transplantation; **EFS:** Event-Free Survival; **GCT:** Germ Cell Tumors; **OS:** Overall Survival; **PBSCT:** Peripheral Blood Stem Cell Transplantation; **PFS:** Progression-Free Survival; **PMNSGCT:** Primary Mediastinal Non-Seminomatous Germ Cell Tumor; **ST:** Single Transplantation; **TT:** Tandem Transplantation; **HDCT:** High-Dose Chemotherapy

## Conclusion

High-dose chemotherapy with tandem autologous transplantation is established as an effective method with low toxicity for treating patients with advanced and recurrent germ cell tumors. An individualized approach, based on precise prognostic assessment and specific selection of pharmacological agents, is crucial for optimizing therapeutic outcomes in this category of high-risk patients.

Early intensification of treatment, especially in cases with extragonadal localization (such as mediastinal non-seminomas) and a high risk of central nervous system involvement, significantly improves the chances of achieving complete remission and long-term survival compared to conventional doses.

Although tandem transplantation has been established as the standard approach for high-risk cases, the results of ongoing clinical trials such as the TIGER trial will be crucial in determining whether further intensification (three or more cycles) is necessary, or whether the current tandem approach continues to offer the optimal balance of efficacy and safety.

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# Рефрактерен лимфом на ходжкин и костномозъчна туберкулоза – клиничен случай и литературен обзор

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# A rare presentation of relapsed/refractory hodgkin lymphoma and bone marrow tubeculosis – case report and literature review

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**РЕЗЮМЕ:**

Едновременната поява на Ходжкинов лимфом и туберкулоза е рядко докладвана находка. Поради сходните клинични симптоми на двете заболявания, като кашлица, фебрилни епизоди и увеличени лифни възли, диагнозата и правилното лечение може да се забавят. Описваме клиничен случай на 48-годишна пациентка с Ходжкинов лимфом, нодуларна склероза съчетан с латентна туберкулозна инфекция. Антитуберкулозно и химиотерапевтично лечение са започнати и е отчетена ремисия. Осем години по-късно се появява късен рецидив на Ходжкинов лимфом с активна HCV инфекция. Започва антивирусно лечение с анти-CD3 антитяло-конюгат. Въпреки това, оценката на PET/CT

**ABSTRACT:**

The concomitant occurrence of Hodgkin lymphoma and tuberculosis is rarely reported. Because of the similar clinical symptoms of both diseases as cough, fever, adenopathy the diagnostic and proper treatment might be delayed. We report a case of a 48-year-old female patient with Hodgkin lymphoma, nodular sclerosis simultaneously with latent tuberculosis infection. Antituberculosis treatment was initiated with chemotherapeutic regimen and remission was detected. Eight years later, a late relapse of Hodgkin lymphoma emerged with active HCV infection. Antiviral treatment was started with anti-CD30 potent antibody-drug conjugate. However, the evaluation of PET/CT described progression of the hematological malignancy

описва прогресия на хематологичното злокачествено заболяване със съпътстваща тромбоцитопения. Биопсията на костния мозък разкрива неспецифично грануломатозно възпаление, предполагащо туберкулозна инфекция.

**Ключови думи:** лимфом на Ходжкин, туберкулоза, химиотерапия, костен мозък

with co-existing thrombocytopenia. The bone marrow biopsy revealed non-specific granulomatous inflammation suspected to be tuberculosis infection.

**Key words:** Hodgkin lymphoma, tuberculosis, chemotherapy, bone marrow

## Introduction

Hodgkin lymphoma (HL) is a rare malignancy that comprises of 15-25% of all lymphomas1 and nearly 1% of the neoplasms worldwide2. The clinical presentation of the hematological disease is usually associated with asymptomatic cervical, supraclavicular and mediastinal lymphadenopathy3. Lately, the therapeutic success in the treatment of HL with response rates above 80% is due to the incorporation of novel combined regimens1. In regards to lymphocyte dysfunction and abnormalities in cell-mediated immunity in HL some patients are susceptible for development of opportunistic infections. Besides, tuberculosis (TB) is crucial infection in immunosuppressed patients with higher mortality rate4. Furthermore, it has been disputed that Mycobacterium tuberculosis may be associated with the occurrence of malignancies, especially lung cancers and lymphomas5-7. Interestingly, clinical overlap may occur due to common symptoms between TB infection and HL rate8. The involvement of the bone marrow with TB is extremely rare disseminated form with incidence range from 0.3% to 3%9. In this article we will present a case of concurrent HL and tuberculosis, with the latter being histologically confirmed in the bone marrow of the patient after HL progression.

## Case Report

A 48-year-old woman was diagnosed with Hodgkin lymphoma – nodular sclerosis by excisional biopsy of abdominal lymph node in June 2015 at the National Hematology Hospital – Sofia, Bulgaria. The initial symptoms included fatigue, low-grade fever and unproductive cough. The physical examination discovered palpable peripheral lymphadenomegaly and splenomegaly. A Computed Tomography (CT) scan revealed enlarged mediastinal and abdominal lymph nodes, and splenomegaly with multiple hypodense regions. Additional investigation of the bone marrow demonstrated normal hematopoiesis. Finally, the diagnosis of HL IIIB clinical stage, IPS 3 (International Prognostic Score) was sustained. Noteworthy, during the diagnostic work up a QuantiFERON test and a Mantoux skin test were carried out because of suspected TB infection and both came out positive. Intensive chemotherapy of 8 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone (BEACOPP) were commenced simultaneously with isoniazid 200mg for the cryptogenic latent TB infection. Therapeutic response was evaluated both after 4 and 8 cycles of chemotherapy. The positron emission tomography (PET) imaging showed complete metabolic response on the interim and end-of-treatment PET/CT scan in June 2016. During the follow-up the HL was in remission although the QuantiFERON test remained positive.

Unfortunately, in May 2023 a late relapse of HL occurred. Multiple metabolically active lymph nodes were discovered in the regions of the right main bronchus, the right hilum and right lung, with varying sizes up to 17mm in diameter with a SUVmax of 14 by a PET/CT scan. Another excisional biopsy was conducted on one of the mediastinal lymph nodes confirming the diagnosis of nodular sclerosis of HL. Although before starting chemotherapy an active hepatitis C virus (HCV) infection occurred with 450,000 copies/ml of HCV RNA. Thus the following treatment included HCV eradication with sofosbuvir/velpatasvir for 12

weeks and brentuximab vedotin (BV) monotherapy 1,8mg/m2 every 3 weeks. After 8 cycles of BV therapy another PET/CT demonstrated progression with multiple mesenteric lymph nodes, new metabolically active paraoesophageal lymph node, mediastinal lymph nodes with no change in metabolic activity or size and new regions in the lower lung lobes with high activity (Deauville score 5). Since March 2024 a therapy with an immune checkpoint inhibitor Pembrolizumab 200mg i.v. every 21 days was initiated. Despite 8 cycles of targeted therapy were accomplished, the disease progressed according to PET/CT evaluation. The investigation showed newly emerged supraclavicular right lymph node (SUVmax 3.6), enlarged mediastinal lymph nodes (paratracheal, precarinal and subcarinal SUVmax 31.5, before SUVmax 3.7)

Then a bone marrow biopsy was performed due to the presence of high metabolic activity on the latter PET/CT and concomitant thrombocytopenia (PLT – 90 G/l). Interestingly, the bone marrow biopsy revealed hypercellularity with proliferation of multiple granulomas without a necrotic center (Figure 1), with giant Langerhans cells with multiple nuclei being also present (Figure 2). The expression of CD30 and CD15 antigens was negative. The granulomas were thought to be most probably due to TB.

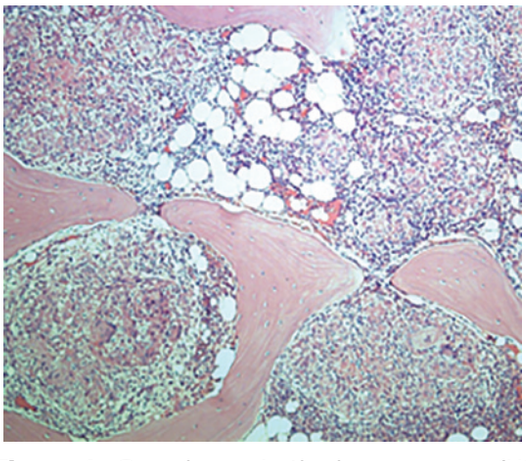

**Figure 1.** *Granulomas in the bone marrow (H&E staining).*

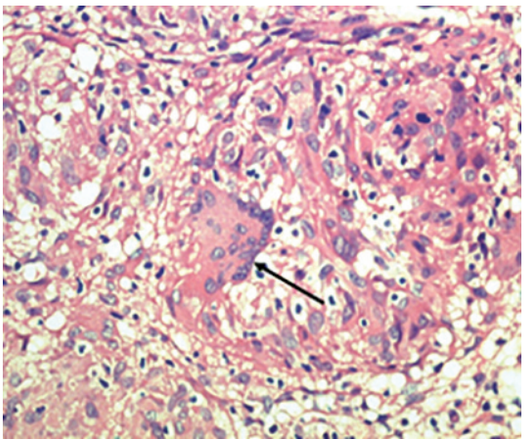

**Figure 2.** *Langerhans cells – giant cell with multiple nuclei (black arrow) in the bone marrow (H&E staining).*

The QuantiFERON test remained positive and a multi-drug course of TB therapy was initiated. A PET/CT scan has been scheduled for the next visit.

## Discussion

Concomitant occurrence of TB and HL is rarely reported. The incidence of TB in Bulgaria declined for a decade from 41.2 to 19.3 cases per 100,000 population in 201810. Hodgkin lymphoma is characterized by bimodal distribution with increased frequency of younger patients and above 55 years11, but our patient was diagnosed at age of 48.

Due to altered immune mechanisms patients with HL are predisposed to development of opportunistic infections including TB12. Besides, the symptoms of the infection and the lymphoid malignancy overlap which may delay the diagnostic process. In our case the lymph node biopsy confirmed the HL diagnosis simultaneously with TB by both positive a QuantiFERON test and a Mantoux skin test. Centkowski et al., discuss that the appearance of Mycobacterium tuberculosis may precede the HL development and promote it13. The hypothesis is based on the direct DNA damage caused by M. tuberculosis, the suppression of the apoptosis and the altered inflammatory microenvironment which advance mutagenesis, combined with angiogenesis favoring tumorigenesis14-15. On the other hand, the changes of cell-mediated immunity, the lower T-lymphocyte count with impaired function,

postponed hypersensitivity response may predispose to a concomitant TB infection in HL12.

Several authors described concomitant occurrence of tuberculosis in HL patients16-17. Despite the lymphadenitis was the most prevalent presentation in TB18-19, some colleagues report other extrapulmonary forms a case of tubercular meningitis20 and bone marrow TB involvement21-25 with concurrent Hodgkin lymphoma. In our case TB was suspected in the bone marrow due to the positive QuantiFERON test and the multiple granulomas that were revealed in the bone marrow biopsy. Although the tuberculin skin test is characterized by low specificity and sensitivity in immunosuppressed patients and granulomas might be observed in HL, in our patient the immunohistochemistry was negative for the antigens CD30 and CD15 and no Reed-Sternberg cells were noticed by the histology investigation.

Besides, during the therapeutic course HCV infection was detected in our patient. A recent investigation confirmed that the HCV also possesses lymphotropic properties due to stimulation of B- and T-lymphocytes26.

**Conclusion**

The association between TB and Hodgkin lymphoma is rarely reported. On the one hand, the tuberculosis may stimulate neoplastic process, while malignancy can result in TB reactivation. However, treating hematological malignancies lead to immunocompromised status which predisposes to infections. The differentiation between both diseases is crucial in order to be initiated optimal treatment in time.

**Abbreviations:**

BV - Brentuximab vedotin
HCV - Hepatitis C virus
HL - Hodgkin lymphoma
HSCT - Hematopoietic stem cell transplantation
IPS 3 - International Prognostic Score
PET - Positron emission tomography
TB - Tuberculosis

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