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Reviewing the current diagnostic and treatment approaches for myocarditis – analysis of literature

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Abstract

Introduction:

Myocarditis is an inflammatory disease of the heart muscle, presenting with symptoms ranging from mild discomfort to severe cardiac dysfunction. It poses diagnostic challenges due to overlap with conditions such as coronary artery disease and its nonspecific presentation. This review summarizes current diagnostic and therapeutic approaches, emphasizing advancements in imaging and personalized treatment strategies.

Aim of the study:

The aim of this study was to summarize the existing knowledge of currently relevant diagnostic and therapeutic approaches to myocarditis, highlighting both established methods and emerging advances.

Materials and Methods:

The literature available in the PubMed database was reviewed using the following keywords: "myocarditis," "myocarditis diagnosis," "myocarditis treatment," "diagnosis of myocarditis," "COVID-19 myocarditis," "viral myocarditis," and "autoimmune myocarditis."

Conclusions:

Myocarditis is a complex and multifactorial condition that requires improved diagnostic tools and individualized treatment strategies. As with other diseases, personalized approaches considering patient-specific factors are essential for better clinical outcomes. To achieve this, further research into innovative diagnostic methods and targeted therapies is necessary. Additionally, raising awareness of myocarditis is crucial for early diagnosis, timely treatment, and patient support.

Key words: myocarditis, viral myocarditis, autoimmune myocarditis, endomyocardial biopsy, cardiac magnetic resonance, immunosuppressive therapy, chest pain.

Introduction

Myocarditis is an inflammatory disease of the heart muscle causing an extensive range of clinical manifestations, from mild features such as fatigue and chest pain to potentially dangerous complications such as cardiogenic shock and life-threatening arrhythmias. The range of clinical presentations is a factor that makes diagnosis of myocarditis difficult because its symptoms may resemble those of other diseases, particularly coronary artery disease (CAD) [1,24]. The global incidence of myocarditis is estimated to range from 10.2 to 105.6 cases per 100,000 people annually, with the highest prevalence observed among men aged 20 to 40 years [2,3]. It is also the third leading cause of death in young adults [4].The etiology of myocarditis is diverse, with viral infections recognized as the leading cause in Western countries. However, the exact role of specific viruses in disease progression remains uncertain, highlighting the need for further research [5,6].Common symptoms include chest pain, shortness of breath, and fatigue, with fever reported in approximately 65% of cases. Prodromal symptoms (e.g. flu-like illness, gastrointestinal illness, sore throat, or respiratory infections) have been shown to be present in 18% to 80% of patients, and typically occur days to weeks prior to the acute phase of the disease [7]. Recent studies reveal that myocarditis frequently progresses to heart failure (HF) and has shown an increase in morbidity and mortality in recent years [8,9]. This highlights the need to improve the accuracy of diagnosis and personalizing the strategy of treatment. Accurate and early diagnosis is of utmost importance since delay in identification can hinder timely and effective therapy.

Etiology

The etiology of myocarditis is complex, encompassing both infectious and non-infectious factors. Among the most commonly identified causes are viral infections, autoimmune reactions, and exposure to toxic substances [10].

Viral infections

Viral infections represent one of the most common causes of myocarditis, with a wide array of viruses implicated. These include Coxsackie B viruses, parvovirus B19, and members of the *Herpesviridae* family, such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Pathological and autopsy studies suggest that viral infections are responsible for up to 69% of clinical myocarditis or pericarditis cases. Enteroviruses, particularly Coxsackie B viruses, are associated with approximately 25% of viral myocarditis cases [8]. Within this group, Coxsackievirus B3 (CVB3) is identified as the most common enteroviral cause of myocarditis [11]. In immunocompetent patients, CMV, HIV, and EBV are rare causes of myocarditis [12]. However, emerging pathogens such as severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 have gained significance. These coronaviruses can directly infect cardiomyocytes via the ACE2 receptor, initiating inflammatory cascades and myocardial cell damage [13]. Additionally, coronaviruses and other viruses like influenza A and B may indirectly cause myocarditis by inducing cytokine-mediated cardiotoxicity or triggering autoimmune responses against cardiac tissues [14]. The underlying pathological mechanisms of SARS-CoV-2-associated myocarditis remain unclear, highlighting the need for further studies involving endomyocardial biopsy (EMB) and autopsy specimens from affected individuals [6].

Bacterial infections

Bacterial infections are a less frequent but important cause of myocarditis. Their prevalence is often debated due to limitations in confirmatory data, such as histological analysis or advanced imaging techniques like cardiac MRI. Nevertheless, bacterial pathogens such as *Borrelia spp.*, *Corynebacterium spp.*, *Streptococcus spp.*, and *Staphylococcus spp.* have been identified as potential causes. Among these, *Staphylococcus aureus* is the most frequently implicated pathogen in bacterial myocarditis [15]. Lyme disease-associated myocarditis, caused by *Borrelia spp.*, is better documented, with an incidence ranging from 0.3% to 4% among individuals diagnosed with Lyme disease. In regions with low vaccination coverage, diphtheria remains a significant bacterial cause of myocarditis, emphasizing the critical importance of timely antimicrobial treatment to manage infections and reduce the risk of severe complications [12]. Although myocarditis resulting from bacterial infections can occur from various pathogens, it remains significantly less common than viral myocarditis [16].

Autoimmune myocarditis

Autoimmune processes play a significant role in the development and progression of myocarditis. Autoimmune myocarditis is caused by an excessive or abnormal immune response, where the immune system mistakenly attacks heart tissue. It is often associated with systemic autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. This immune reaction leads to the infiltration of the myocardium by T lymphocytes, macrophages, and other inflammatory cells, causing inflammation and myocardial damage [17]. One particularly aggressive subtype, giant cell myocarditis, often progresses to dilated cardiomyopathy and heart failure and is typically resistant to treatment [18]. Another form, eosinophilic myocarditis, occurs in the context of hypereosinophilia or autoimmune diseases, where eosinophilic infiltration severely damages heart tissue, resulting in a poor prognosis [19]. Chronic lymphocytic myocarditis represents another variant, where prolonged inflammation leads to myocardial fibrosis and a gradual loss of cardiac function. Additionally, granulomatous myocarditis, commonly seen in sarcoidosis, causes significant cardiac damage as well as systemic complications involving organs such as the lungs and kidneys [17].

Drugs and toxins

Myocarditis can be caused by various drugs and toxins that lead to myocardial inflammation and damage. Among the most commonly implicated medications is clozapine, which is associated with myocarditis, particularly in the early weeks of therapy. Chemotherapy agents such as doxorubicin and trastuzumab are also significant contributors due to their cardiotoxic effects, often resulting in inflammatory responses and myocardial injury [20]. Rare cases of myocarditis have been linked to vaccines, including influenza vaccines, although further research is needed to better understand their potential impact on the heart [21]. Other medications, such as tricyclic antidepressants, catecholamines, and agents used in radiotherapy, may also increase the risk of myocarditis by causing direct myocardial toxicity. Environmental toxins, such as heavy metals (lead, mercury, arsenic), along with substances like cocaine, amphetamines, and alcohol, play a significant role in toxin-induced myocarditis. These substances can trigger myocardial inflammation through mechanisms such as vasoconstriction, ischemia, and direct toxicity to cardiomyocytes, ultimately leading to compromised heart function [22].

Diagnosis

Endomyocardial biopsy (EMB) remains the gold standard for confirming myocarditis. However, its invasive nature and associated risks limit its widespread use, and it is often underperformed or unavailable in many hospitals. The development of new, noninvasive diagnostic tools enabled broader detection of patients with clinical suspicion of myocarditis, including those with more favorable prognosis [23]. According to the latest HF guidelines, the suspicion of acute myocarditis is based on a clinical presentation and ≥ 1 mandatory diagnostic test (preferably CMR) that yields a positive result, while excluding alternative explanations, such as coronary artery disease or valvular abnormalities, for cardiac failure. To make this overview of available diagnostic approaches clear, it will be structured in the format according to the recent HF guidelines: clinical presentation, mandatory diagnostic tests, and additional diagnostic tests [24].

Clinical presentation

Myocarditis can range from being completely asymptomatic to presenting with mild symptoms or progressing to severe, life-threatening conditions. Clinical manifestations include chest pain with preserved left ventricular ejection fraction (LVEF) and absence of arrhythmias, worsening or chronic heart failure, fulminant myocarditis with cardiogenic shock and reduced LVEF, as well as critical arrhythmias or conduction disturbances, such as ventricular arrhythmias, atrioventricular block, or sudden cardiac arrest [3,25]. Findings from the European Study of Epidemiology and Treatment of Inflammatory Heart Disease, which assessed 3055 patients with suspected acute or chronic myocarditis, showed that 72% experienced dyspnea, 32% reported chest pain, and 18% presented with arrhythmias. Other symptoms may include reduced exercise capacity, palpitations, and syncope, underscoring the diverse nature of the disease's cardiac presentations [26].

Mandatory diagnostic tests:

ECG

An electrocardiogram (ECG) is recommended as an initial screening tool for patients presenting with cardiac symptoms, although its sensitivity for diagnosing myocarditis is limited [27]. Common ECG changes in myocarditis, while often nonspecific, do not rule out

the condition if absent. The most frequently observed abnormality is diffuse concave ST-T segment elevation, which may appear in inferolateral leads or across multiple leads [25]. Additional findings include repolarization disturbances, pathological Q waves, T-wave abnormalities, prolonged QRS duration, conduction blocks, and frequent premature ventricular contractions. These abnormalities reflect the diverse cardiac involvement seen in myocarditis and are useful indicators, although not definitive for diagnosis [27,28,29]. Such conduction abnormalities, particularly atrioventricular or intraventricular blocks, may suggest underlying conditions like cardiac sarcoidosis, giant cell myocarditis, or advanced inflammation [30].

Laboratory tests

Cardiac troponin levels are a critical marker of myocyte injury and should be routinely evaluated in patients with suspected myocarditis. High-sensitivity troponin assays are particularly useful, offering greater accuracy in detecting myocarditis compared to conventional troponin tests [31]. However, troponin elevation may not always be present, especially during the chronic phase of the disease [32]. In a similar way, white blood cell (WBC) count, including a differential to assess eosinophil levels, is a standard test in suspected myocarditis. Elevated peripheral eosinophils are often seen in eosinophilic myocarditis, although a normal WBC count does not exclude the condition. Evaluating WBC morphology and eosinophilia is essential for excluding other potential causes of inflammation [33].

Echocardiography

Echocardiography is a crucial diagnostic tool for assessing ventricular function, cardiac structure, and potential complications in myocarditis, such as myocardial edema, segmental hypokinesia (inferolateral/inferior regions), and pericardial effusion [36]. Early evaluation is particularly important, as 75% of patients initially present with a normal-sized left ventricle and preserved systolic function. However, rapid cardiac deterioration may occur, necessitating repeat echocardiograms in response to clinical changes [34]. In addition to its role in ruling

out non-inflammatory causes of symptoms and detecting complications like fluid accumulation, thrombi, or valvular regurgitation, advanced echocardiographic methods such as speckle tracking echocardiography (STE) can identify subclinical myocardial dysfunction at early disease stages. STE is especially recommended for diagnosing acute myocarditis in patients with preserved left ventricular ejection fraction (LVEF). This technique offers high sensitivity and demonstrates strong correlation with findings from endomyocardial biopsy (EMB) and modern cardiac magnetic resonance (CMR) imaging approaches [35].

Cardiac magnetic resonance imaging (cMRI)

Cardiac magnetic resonance (CMR) imaging is advised for all patients with a clinical suspicion of myocarditis who exhibit elevated biomarkers or ECG or echocardiographic abnormalities suggestive of myocardial injury. While CMR serves as an alternative to endomyocardial biopsy (EMB), it is important to note that it cannot identify the underlying cause of the condition [36]. CMR is a valuable non-invasive tool for detecting myocardial inflammation, particularly in hemodynamically stable patients, reducing the need for invasive procedures like coronary angiography or endomyocardial biopsy [37]. Its sensitivity depends on the degree of cell necrosis and the clinical presentation, which makes it less reliable in certain clinical scenarios [38]. Detection, quantification, and localization of edema, inflammation, and fibrosis are achieved through T1- and T2-weighted mapping techniques, along with evaluations of extracellular volume and late gadolinium enhancement (LGE) [24]. Furthermore, CMR is unable to identify infectious agents within the myocardium or analyze immune cell infiltrates, which are essential for assessing prognosis and planning appropriate management [28]. A combination of techniques, such as CMR and troponin measurements, enhances the precision of diagnosis [39].

Additional diagnostic tests:

Endomyocardial biopsy (EMB)

Endomyocardial biopsy (EMB) remains the gold standard for diagnosing myocarditis, offering definitive confirmation by detecting infectious agents (such as viral genomes) and identifying immune cell infiltrates [23]. According to the ESC working group on myocardial and pericardial diseases, acute myocarditis is diagnosed through EMB by the presence of myocyte necrosis and myocardial inflammation, confirmed via immunohistochemical

detection of ≥14 immune cells/mm², including CD3+ T-lymphocytes and/or CD68+ macrophages. In chronic myocarditis, inflammation and interstitial fibrosis are typically observed in the absence of acute myocyte injury [40]. EMB also allows for the evaluation of the myocardium's histotype, immunological profile, and virological status using advanced techniques like immunohistochemistry and polymerase chain reaction (PCR) analysis [41]. The procedure is invaluable for identifying specific types of myocarditis, such as lymphocytic or eosinophilic myocarditis, and provides crucial insights into prognosis and cardiovascular pathophysiology [22,42]. It is particularly recommended in patients with severe cardiac dysfunction, serious ventricular arrhythmias, or atrioventricular blocks, as well as those unresponsive to standard heart failure or antiarrhythmic therapy. EMB facilitates tailored treatment by uncovering the underlying etiology in cases such as giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, or systemic inflammatory diseases. It may also be repeated to assess unexplained progression of heart failure or to monitor response to treatment [24]. Endomyocardial biopsy is increasingly used in patients with systolic or diastolic dysfunction due to its safety profile. When performed by experienced cardiologists, the risk of major complications is below 1%. Biventricular EMB, in particular, is associated with a minimal complication rate [43]. Moreover, endocardial electroanatomic mapping can guide targeted EMB, especially in cases of suspected cardiac sarcoidosis or giant cell myocarditis, enhancing diagnostic precision [44]. While cardiovascular magnetic resonance (CMR) remains a key diagnostic tool, EMB is an essential supplementary method for diagnosing unexplained or rapidly progressing myocarditis, as it provides detailed insights that CMR alone cannot achieve. Advanced imaging techniques, such as FDG-PET, may complement EMB, particularly in cases where CMR accuracy is limited, further improving diagnostic accuracy and enabling better management of myocarditis [41].

Cardiac PET

Cardiac PET imaging, particularly 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), has emerged as a valuable tool in the diagnostic evaluation of myocarditis and related conditions. This technique enhances diagnostic precision by detecting myocardial inflammation through elevated glucose uptake in affected regions. It is particularly useful in patients where cardiac magnetic resonance (CMR) is not feasible or contraindicated, such as those with suspected systemic autoimmune diseases or cardiac

sarcoidosis [6,25]. FDG-PET also serves as an effective complement to CMR, especially in chronic myocarditis cases where CMR accuracy may be limited [45]. Combining 18F-FDG PET with cardiac MRI in select myocarditis cases can provide deeper insights into disease progression, offering a more comprehensive understanding of myocardial pathology and treatment response. In the context of cardiac sarcoidosis, FDG-PET plays a pivotal role in both diagnosis and monitoring treatment effectiveness, making it an indispensable tool in managing these complex conditions. Hybrid imaging approaches, such as PET/MRI, are increasingly recognized for their ability to integrate metabolic and anatomical data, further advancing diagnostic accuracy and guiding therapeutic decisions [45,46].

Coronary angiography or computed tomography coronary angiography (CTCA)

In the diagnostic evaluation of suspected myocarditis, it is essential to exclude major coronary artery disease (CAD) or acute coronary syndrome (ACS), that can present similarly. Coronary angiography or CTCA plays a critical role in ruling out these pathologies. Moreover, these methods may help identify extracardiac sources of manifestations, such as systemic or inflammatory disorders, contributing to a more accurate diagnosis [24].

Additional laboratory tests

Inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often elevated in myocarditis, with CRP being elevated in 80–90% of patients [47,48]. However, these markers lack specificity, as they are also commonly elevated in conditions such as acute pericarditis, which limits their diagnostic value. While they can support the diagnosis, their role is supplementary and not definitive [47]. Measurement of brain natriuretic peptides, including NT-proBNP, may also assist in evaluating cardiac dysfunction but lacks specificity for myocarditis, as normal results do not rule out the condition [28]. Screening for autoimmune diseases is recommended in patients with clinically suspected myocarditis to identify potential systemic causes. Routine viral serologic testing is generally not indicated, as a positive result only reflects immune system interaction with an infectious agent, rather than confirming myocardial infection. Exceptions include specific infections, such as hepatitis C, rickettsial diseases, HIV, *Borrelia burgdorferi*, or *Trypanosoma cruzi* [28]. Serum cardiac autoantibodies may be assessed in specialized centers, but such tests are not widely available or commercially validated [23,28]. A newly identified circulating

microRNA (hsa-miR-Chr8:96), synthesized by type 17 helper T cells, has shown the potential to differentiate myocarditis from acute coronary syndrome, myocardial infarction, and healthy controls. This promising biomarker may aid in the early diagnosis of myocarditis; however, further validation in broader clinical settings is required before it can be incorporated into routine practice [49].

Treatment

Hospitalization is recommended for all patients with suspected or confirmed acute myocarditis to ensure proper diagnosis and assessment of disease severity [36]. According to the latest ESC HF guidelines, the management of myocarditis should be guided by the clinical presentation, stage of the disease, and, when identified, its underlying cause [24]. Individualized therapy should also rely on findings from endomyocardial biopsy (EMB), which provide critical information for selecting immunosuppressive or anti-infective treatments and for evaluating therapeutic effectiveness [24].

Heart failure management

Heart failure therapy should be initiated in patients with reduced left ventricular ejection fraction (LVEF) at diagnosis and continued for at least six months after recovery, defined as an ejection fraction (EF) above 50% [24]. Recommended treatments include angiotensin-converting enzyme inhibitors, angiotensin receptor neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter type 2 inhibitors, in line with current guidelines [24]. Patients with hemodynamic instability, including those with acute or fulminant myocarditis, require care in specialized intensive cardiac units. Severe ventricular dysfunction or cardiogenic shock may necessitate advanced support such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or the Impella heart pump, which can serve as a bridge to recovery or transplantation [3,50,51]. Initial management typically involves pharmacological therapy, including diuretics, inotropes, and vasopressors, with mechanical circulatory support implemented if these measures prove insufficient [51].

Arrhythmia management

Specific guidelines for arrhythmia management in myocarditis are lacking, and treatment should align with established protocols for arrhythmias and device implantation after the

acute phase [3]. Pacing may be necessary for complete atrioventricular block, while implantable cardioverter-defibrillators (ICDs) are generally delayed until 3 to 6 months after the acute phase resolves. A wearable cardioverter-defibrillator may be used as a temporary measure during this period [3]. However, in cases of sustained ventricular tachycardia or ventricular fibrillation causing hemodynamic instability, ICD implantation may be considered even during the acute phase [52,53]. For patients with chronic myocarditis or those recovering from myocarditis experiencing recurrent ventricular tachycardia, treatment options include amiodarone, catheter ablation (if amiodarone is ineffective or poorly tolerated), and/or ICD implantation [44].

Pharmacological and immunosuppressive therapies

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in uncomplicated acute myocarditis remains controversial and is not routinely recommended [28]. For patients with myocarditis accompanied by pericardial involvement, colchicine is suggested as an effective therapeutic option [54].

Immunosuppressive therapy can be an option for patients with chronic myocarditis confirmed through endomyocardial biopsy (EMB), provided there is no evidence of active viral infection [24]. For eosinophilic myocarditis, after ruling out causes such as medications or parasitic infections, early treatment with glucocorticoids alone or in combination with azathioprine and/or cyclosporine is essential. Similar strategies are also applied to cases of giant cell myocarditis and cardiac sarcoidosis. In contrast, specific treatments are not available for lymphocytic myocarditis, except in cases associated with systemic diseases or immune checkpoint inhibitors [3]. Giant cell myocarditis, known as the most aggressive form of autoimmune myocarditis, requires the immediate initiation of high-dose immunosuppressive therapy once diagnosed [55]. Eosinophilic myocarditis often responds positively to high-dose steroid therapy, alongside the discontinuation of any triggering agents [56]. There is also promising evidence supporting the use of prednisone and azathioprine for managing chronic lymphocytic myocarditis [25]. In patients with fulminant myocarditis presenting with acute heart failure or life-threatening arrhythmias, immediate empirical therapy with intravenous corticosteroids should be considered when an immune-mediated cause is suspected. This approach is particularly applicable to patients with cardiogenic shock, severe ventricular arrhythmias, or advanced atrioventricular block of autoimmune origin. The European Society

of Cardiology recommends follow-up viral genome testing on EMB samples, as reactivation of a viral infection may require discontinuation of immunosuppressive therapy [24,57].

Immunomodulatory therapy

High-dose intravenous immunoglobulins (IVIG) have been proposed as a potential therapy for acute myocarditis due to their immunomodulatory and anti-inflammatory properties. Nonetheless, results from two clinical trials investigating IVIG in myocarditis have been inconclusive [58,59]. Current evidence does not support the routine use of IVIG as a standard treatment for myocarditis [24].

Anti-infection therapy

Currently, no antiviral therapy has demonstrated proven efficacy in myocarditis. However, targeted antiviral treatment is recommended in confirmed infections, such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), or human herpes virus 6 (HHV-6), especially in cases with high viral load or active viral replication. Additionally, when other treatable infectious diseases, such as Lyme disease, are identified, appropriate specific therapy should be administered [24]. Telbivudine and intravenous immunoglobulin (IVIG) have shown potential as therapeutic options, but further research is needed to confirm their effectiveness [54].

Recovery monitoring and safe return to physical activity

To reduce the risk of exercise-related sudden cardiac death (SCD) following myocarditis recovery, assessment using ECG, imaging studies, exercise stress testing, and Holter monitoring is recommended. Follow-up should occur at planned intervals, with an initial evaluation 3–6 months after the acute phase and annually for at least 4 years [60]. Intense sporting activities should be avoided until symptoms resolve, cardiac enzymes normalize, and ECG or imaging abnormalities disappear. A minimum restriction period of 6 months following complete recovery is advised [24,60].

Conclusions

Myocarditis is a complex condition with diverse causes, variable presentations, and significant diagnostic challenges. Despite advancements, accurate diagnosis remains difficult, particularly in subtle or overlapping cases. Endomyocardial biopsy (EMB) remains the gold standard for confirming myocarditis, allowing identification of myocardial inflammation and etiological triggers, though its invasive nature limits widespread use. Non-invasive imaging techniques, such as cardiac magnetic resonance (CMR), play a crucial role in detecting myocardial edema, fibrosis, and inflammation, providing valuable diagnostic insights while complementing EMB. Treatment is primarily supportive, focusing on managing complications. In some cases, immunosuppressive therapies are necessary. When an etiological trigger is identified, targeted treatment may be considered where appropriate. Continued advancements in diagnostic methods and personalized treatments are vital for improving patient outcomes, reducing morbidity, and addressing the complexity of this disease.

Disclosure

Author's contribution

Conceptualization: Damian Zys and Maciej Wojszczyk; Methodology: Julia Ryniecka and Michalina Wójcikiewicz; Software: Filip Arczewski and Maciej Wojszczyk; Check: Julia Kulbacka and Marta Chuncia-Ileczko; Formal analysis:Julia Kacperczyk; Investigation: Witold Czyż; Resources: Julia Kulbacka; Data curation: Julia Ryniecka and Filip Arczewski; Writing – rough preparation: Damian Zys and Julia Kacperczyk; Writing – review and editing: Karol Dziedzic and Marta Chuncia-Ileczko; Visualization: Michalina Wójcikiewicz and Karol Dziedzic; Supervision: Witold Czyż; Project administration: Damian Zys; Receiving funding - no specific funding. 10 All authors have read and agreed with the published version of the manuscript.

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