REVIEW ARTICLES

https://doi.org/10.52418/moldovan-med-j.64-2.21.13
UDC: 616.124-008.46:616.74-007.17-053.2

Cardiomyopathy secondary to Duchenne muscular dystrophy in children

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Manuscript received January 11, 2021; revised manuscript April 12, 2021; published online April 28, 2021

Abstract

Background: Cardiomyopathy (CM) associated with Duchenne muscular dystrophy (DMD) is a commonly recognized appearance of this neuromuscular disease, significantly increased morbidity and mortality, as well as the necessity for cardiological management. CM in DMD is defined by left ventricular (LV) systolic dysfunction and both atrial and ventricular dysrhythmias and is associated with higher mortality than other cases of pediatric dilated CMs. Notwithstanding the high rate of cardiac involvement, patients are usually asymptomatic despite significant LV dysfunction, because of likely poor mobility that masks the usual heart failure (HF) symptoms. Also, imagistic predictors are provided to be very helpful in defining early LV dysfunction, especially electrocardiogram and cardiac imaging (transthoracic echocardiography, speckle-tracking, cardiac magnetic resonance) are used to detect the onset and progression of dilated cardiomyopathy (DCM) in DMD.
Conclusions: As most DMD patients are asymptomatic for a long time of their life, so identifying predictors of HF is crucial to support these patients. Ventricular dysfunction based on the ejection fraction (EF) measurement helps to choose therapy. In the case of early DCM (LVEF≥50%) the great purpose is to prevent ventricular dysfunction incipience with first-line HF therapy with Angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs). Current guidelines recommend the use of conventional HF medication in case of disease progression and DCM with Mid-Range Reduction of LV EF (40-49%). The therapeutic approach for patients with DCM and severe ventricular dysfunction (<40%) has been studied less profoundly and contemporary guidelines recommend all drugs used for HF treatment.
Key words: Duchenne muscular dystrophy, cardiomyopathy, heart failure, neuromuscular.

Cite this article
Rodoman I, Palii I, Sacara V, Gladun S. Cardiomyopathy secondary to Duchenne muscular dystrophy in children. *Mold Med J.* 2021;64(2):70-78. https://doi.org/10.52418/moldovan-med-j.64-2.21.13.

Introduction

Duchenne muscular dystrophy (DMD), defined more than 150 years ago, is the most widespread type of muscular dystrophy in children, affecting 1:3500/5000 liveborn boys [1, 2]. DMD belongs to the group of dystrophinopathies, affected by genetic mutations in the gene that codes for dystrophin and defined by variable degrees of skeletal and cardiac muscle impairment. Typically, DMD is the most severe form while Becker muscular dystrophy (BMD) is more benign form along with the X-linked DCM (XL-DCM) and the cardiomyopathy of DMD/BMD carriers [3-5].

Mutations linked to the dystrophin gene occur in the short arm of the X chromosome (Xp21.1), which describes the largest known gene, composed of 79 exons [6, 7]. Mutations causing a shift in the open reading frame occur in the lack of dystrophin, leading to the DMD phenotype. X-linked recessive inheritance model is typical for this disease; a mother-carrier has a 50% chance of transmitting it to her boys. Although most DMD mutations are inherited, spontaneous mutations can happen in up to 30% of cases [8].

The major presenting manifestation of DMD is skeletal muscle weakness. Notwithstanding a family history, this diagnostic should be suspected in boys manifesting gait disturbances occurring between two and five years of age, followed by proximal weakness, delayed psychomotor development, calf hypertrophy, and high levels of liver transaminases. The primary screening includes the dosage of the enzyme creatine phosphokinase (CPK), which is usually high (> 2000 U/L). Confirming tests range according to availability, but they embrace genetic tests that show specific gene mutations (deletions, duplications, point mutations) or muscle biopsy revealing the deficiency of dystrophin [9].

However, the heart muscle is affected by multiple muscular dystrophies. Cardiomyopathy associated with DMD is a commonly recognized appearance of this neuromuscular disease, significantly increased morbidity and mortality, as well as the necessity for cardiological management [10]. Progressive muscular damage leads to increasing muscular weakness and motor dysfunction, motor development delays, and impairment in respiratory and cardiovascular

function. Until recently, respiratory failure secondary to neuromuscular dysfunction was the most common reason for death, but at the moment dilated cardiomyopathy (DCM), arrhythmias, and congestive heart failure (HF) represent the most life-limiting heart condition in DMD [9, 11, 12]. Nevertheless, the development of respiratory care across the last few years has made cardiomyopathy (CM) an increasing cause of morbidity and mortality in DMD patients [13-15].

DMD DCM is described by left ventricular (LV) systolic dysfunction and arrhythmias, which are allied with higher mortality than other cases of pediatric dilated CMs. Quick detection and management are associated with postponed progression of LV dysfunction and advance in results. However, DMD CM remains underrecognized and undertreated broadly because the symptoms of heart failure in these patients are frequently neglected and not clinically apparent [16].

Epidemiology

The prevalence of DMD in the USA, Australia, England, and Canada is estimated to be 1 per 3500 to 50000 male births [17]. But according to the data of Sacară et al. the frequency of DMD/BMD is 9.13:100000 for the Republic of Moldova [18, 19]. The DMD onset mean age is 3–5 years and patients usually remain in the non-ambulatory stage till the age of 10–12 [15, 16]. The symptomatic HF incidence is rare early in childhood but increases at the age 10-20. Prospective studies have estimated the prevalence of DCM and noted it in the third of the patients under 14 years, half in those who were 18 years old, and almost all patients who were older than 18 years [14-17]. There have also been records of patients with X-linked DCM with low clinical evidence of skeletal muscle disease due to compensatory upregulation of the brain (B) isoform in skeletal muscle but not cardiac myocytes, although this is a unique phenotype [12, 20]. Female carriers have a chance to be influenced by this disease, although men manifest cardiac dysfunction at a significantly more youthful age than women. The awaited life prognosis with modern therapies, such as assisted ventilation is 25–30 years of age [15, 16].

Pathophysiology of DMD DCM

DMD is caused by mutations in the dystrophin gene that result in the reduction or absence of the sarcolemmal protein dystrophin, a protein that plays a fundamental role in the cytoskeleton of muscle cells by attaching intracellular structures with the extracellular matrix [21]. Some pathomechanisms have described cellular impairment initially caused by the absence of dystrophin, in both skeletal and cardiac muscles.

Dystrophin is located on the cytoplasmic side of cardiac and skeletal muscle sarcolemma and contributes to structural maintenance. It is a component of a larger glycoprotein complex and is also involved in cellular regulation and signal transduction. In cardiac muscle, the lack of dystrophin ends in instability and progressive degeneration of the muscle fibers through membrane vulnerability with continuous muscle compressions [22, 23].

Ordinarily, dystrophin presents structural maintenance for the myocyte and sarcolemmal membrane by its binding of actin at the C amino-terminus with the dystrophin-associated protein complex and sarcolemma at the carboxyl-terminus and the extracellular matrix of muscle [6, 24].

Dystrophin is additionally existing in the T-tubular membranes of cardiac myocytes and is implicated in the supporting of membrane stability and transduction of mechanical energy from the sarcomeres to the extracellular matrix. The loss of the dystrophin guides to an extreme vulnerability of the cellular membranes; cellular stress could be immediately interfered with by the absence of dystrophin, or obliquely via intracellular Ca2+ overload or oxidative stress.

Abnormal calcium handling due to the lack of dystrophin is believed to perform a significant function in the pathogenesis. Damage of cell membrane integrity and formation of breaks may result in high calcium levels in muscle fibers. Stretch-activated channels may perform abnormally leading to increased calcium entry. Elevated cytoplasmic calcium may activate proteases, such as calpain and increase the generation of reactive oxygen varieties producing injury to cellular proteins and membranes [25, 26]. Reactive oxygen kinds activate NF-KB pathways directing to increased pro-inflammatory cytokines. Inflammation may be harmful, promoting additional muscle degradation and necrosis [25, 26].

The generation of these damaging cellular pathways and Ca2+ pathways manage to dystrophic DCM [27]. As muscle syndrome advances, skeletal and cardiac myocytes necrotize, and mechanisms of repair are also not enough, with consistent gradual replacement by fibrofatty tissue [28].

DMD DCM is marked by a weaker LV wall and its progressive dilatation, reflecting the continuing myocyte damage [9, 29]. In particular, the constant mechanical stress manages to apoptosis and fibrotic replacement and scarring that progresses from the epicardium to the endocardium, starting at behind the posterior region and mitral valve apparatus. This scarring develops downward progressively via the apex and around the heart, finally attending to DCM [30-32].

Disease predictors

Contemporary 2018 DMD Care Guidelines estimated that regular cardiac follow-up is crucial for care [16]. From the time of the final diagnosis, all energy should be directed to detect the early incipience and the progression of the DCM, which is very challenging.

Notwithstanding the high rate of cardiac involvement, patients are usually asymptomatic despite significant LV dysfunction, because of likely poor mobility that masks the usual HF symptoms. Dyspnea on exertion or decreased exercise capacity goes unnoticed due to concomitant skeletal muscle weakness. Orthopnea and paroxysmal nocturnal dyspnea can be missed due to the use of nocturnal non-invasive mechanical ventilation for rest [15, 16, 33].

Early identification is so important for treatment, conditioning the life expectancy. In the non-ambulatory stage, an

asymptomatic patient's continuing check-up is necessary to determine the progress of the disease. Clinical examination remains difficult because of low BP rates, cool extremities due to reduced skeletal muscle mass. Therefore, these clinical features require a multidisciplinary evaluation to distinguish ongoing of the cardiac process.

However, enhanced survival of patients with DMD has contributed to an increase in overall the incidence and prevalence of CM [15]. Early detection is a key in preventative treatments that can delay the progressive deterioration in cardiac function and the start of overt HF symptoms.

Several biomarkers are currently used in the diagnosis and monitoring of cardiac disease. One such biomarker is cardiac troponin I, which is discharging during myocardial cell injury and classically utilized for the diagnosis and evaluation of myocardial infarctions. Also, serum biomarkers are provided to be very helpful to define HF and are currently used to evaluate the functional state in adult and pediatric patients.

Electrocardiogram and cardiac imaging are also routinely used to detect the onset of DCM and its progression [29]. These non-invasive tests provide useful information about the ventricular function, both systolic and diastolic ones.

Cardiomyopathy in DMD is described by progressive fibrosis in LV finalizing into its dysfunction and dilatation [9]. Echocardiographic precursors of cardiac dysfunction appear in 10-20 years of life and are almost completely present in all adults [33]. So, the investigation into recognizing additional, potentially modifiable predictors for CM progression is limited. Studies in *mdx* mice, a mouse model of DMD, show that dystrophin-lacking myocardium is more exposed to pressure overload of the LV than normal one [34]. Increased LV afterload may pose the already weak myocardium of DMD patients at risk for accelerated myocardial dysfunction. LV afterload is influenced by hypertension, obesity, and aortic stiffness [35].

DMD DCM and other comorbidities

Some studies have distributed cross-sectional data on the prevalence of hypertension in DMD patients [36-38]. Ricotti et al. found hypertension in 5% of the patients aged 3–15 years on steroids while in a study by Braat et al. 45% of the patients had hypertension [37, 38]. Wong et al. reported that 25.5% of patients on daily steroids aged 10–13 years had systolic hypertension [36]. In patients aged 13–16 years, they reported systolic hypertension in 10.3% of patients. One study described a correlation between low blood pressure (BP) ranges and younger age in DMD with Hispanic origin as an involving predictor [39].

Obesity is commonly found in DMD due to corticosteroids using and low mobility [40]. Prevalence of obesity has been described in up to 73% DMD patients on steroid treatment <13 years and higher body-mass index (BMI) was correlated with longer duration and greater cumulative dose in ambulant DMD patients utilizing prednisone [41, 42]. Increased BP is a well-known side outcome of corticosteroids [43]. But its utilization has led to the ambulant stage prolongation in DMD by almost 3 years [44]. It has also been correlated with a delayed onset of DMD-related cardiomyopathy [45, 46]. Corticosteroid treatment is thus an essential part of the standards of care in DMD and is prescribed from the age of 4 to 5 years onward. Extensive research analyzing BP values in DMD patients with and without steroids will therefore not be feasible, and the high percentage of patients on steroids in this study may well be the cause that steroid use was not an objective factor in the linear mixed model.

In N.M. van de Velde et al. study increased BMI, but not systolic BP was linked to early myocardial deformation defined by peak systolic global longitudinal strain (GLS) in young DMD patients < 11 years of age. The results of this study propose that factors influencing afterloads, such as increased BP and BMI, may play an important role in the degeneration of cardiac function in DMD [47].

Genotype-phenotype correlations in DCM-DMD

The dystrophin gene is the largest gene identified in humans, and its complexity and correlation to phenotype remain to be analyzed [48]. Inheritance is in an X-linked recessive manner. Genetic mutations are generally out of the frame and cover duplications, deletions, frameshift (nonsense and splice), missense, and premature stop codon [49]. Numerous attempts were tried to order DMD patients based on their genotype. Where the mutation happens within the gene has some correlation for cognition (i. e. mutations upstream of exon 30 correlates with spared cognition), but not motor function [50].

There are limited data correlations in genetic mutations and CM in DMD. It is still an open question whether variations in genotype indicate myocardial dystrophin expression, and consequently what impact they will produce on cardiac function. Therefore, Jefferies et al.'s study proved that mutations in exons 12 and 14 - 17 were associated with cardiomyopathy but mutations in exons 51 and 52 appeared to be protective against cardiac involvement [51]. However, other researches using different techniques have been uncertain [49].

Biomarkers in DMD DCM

Cardiac troponin may be a predictor of CM secondary to DMD. Troponin I is released in the circumstances of DMD heart disease, likely as a consequence of membrane integrity loss rather than a primary ischemic etiology, but there are contradictory results about their diagnostic and prognostic involvements in the DMD DCM [52-54].

High cardiac troponin levels are strongly correlated with left ventricular dysfunction and may indicate the progression of the cardiomyopathy when acute chest pain is present [55]. It also seems to correspond with the conclusion of myocardial fibrosis on cardiac MRI [56].

Recently, one study revealed that troponin I levels were significantly elevated in patients with moderate late gadolinium enhancement (LGE) related to no LGE and constant over all ages, and it is interesting, that absence of positive correlation among mild-to-severe LGE and troponin is presumably because of a reduced dystrophin amount at advanced disease stages when most of the heart muscle has already been replaced by conjunctive tissue. Therefore, tro-

ponin I could provide valuable data to control patients in the clinical practice, and extra studies are needed [56].

Based on the above, troponin can be a valuable minimally invasive outcome marker to find early myocardial disease implications and understand the origin of damage in DMD CM.

High left atrial pressure as a consequence of pulmonary hypertension and LV dysfunction induced by respiratory muscles impairment are supposed to be implicated in appearing of high levels of plasma natriuretic peptide in DMD. In patients with a non-ambulatory stage of DMD was observed mild or marked elevation of alpha-ANP levels being a sign of a lower prognosis and may be a useful predictor for disease management [57]. Villa et al. in their study reported a meaningful association among cystatin C, eGFR, and heart muscle dysfunction, contributing to the newest predictor to confirm cardiorenal syndrome in children with DMD [58].

In Carol A. Wittlieb-Weber et al. study, BNP levels measured before dying or research end were significantly higher for those patients who died compared to those living at research finish [59]. These conclusions are compatible in Cheeran et al. study, who investigated a cohort of 43 DMD patients with CM, and discovered predictors in comparing the non-living to the living cohorts including lower BMI, maximum inspiratory pressures, and cardiac serum biomarkers [60].

Imagistic predictors in DMD DCM

Electrocardiographic abnormalities

Electrocardiographic (ECG) follow-up is obligatory and valuable for the cardiological evaluation of DMD patients. Electrocardiographic irregularities commonly found in patients with DMD can correspond to fibrotic alterations seen on pathology expertise [16, 61]. But, according to some reports, the ECG frequently does not correlate with CM development [62]. In the process of LV function failing, it is possible to find more frequently sinus tachycardia, supraventricular and ventricular arrhythmias. In Fayssoil et al. study bundle branch block is a significant predictor for cardiac situations, while patients with low dystrophin level show an increased incidence of cardiac events [63].

There can be different changes on a traditional ECG: sinus tachycardia, short PR, high R waves in right precordial derivations, right ventricular hypertrophy, and Q waves in left lateral and precordial leads (D1, aVL, V5, V6), narrow and deep Q waves. The sinus tachycardia phenomenon is the most described finding in DMD. It is also essential to remark that RSr' pattern and high R waves in V1 can be normal in childhood, with no association with heart disease [64]. Also, there are some data about the correlation between the left bundle branch block and mortality in adult patients on mechanical ventilation [63]. Significant arrhythmias in the 24-h Holter ECG, especially atrial and ventricular tachycardias, were uncommon findings in patients with ejection fraction (EF) more than 35% and had low clinical applicability in patients with preserved EF [65].

Transthoracic Echocardiography/ Speckle-Tracking

Echocardiography performs the main function in LV dysfunction identification and also dynamic evaluation is required. According to the literature, local anomalies of LV function may be resolved by other imaging investigations, such as speckle tracking echocardiography (STE) or cardiac magnetic resonance (CMR) [66]. Dilated LV is assessed via standard deviations, estimated with Z-scores compared with age, BMI in DMD patients. LV dysfunction is considered lower than 55%, and fractional shortening (FS) lower than 28% [67, 68].

Correlation of 2D and 3D echo techniques for LV end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) was significantly positive, but 3D LVEDV and LVESV were lower in comparison with 2D outcomes; while, LV EF estimation was similar in two methods [69]. According to some reports, FS is rated the best evaluator of LV systolic function, because of its independence of age and magnitude of measures [70]. In the matter of diastolic function, in DMD patients can be found the followuing echocardiographic abnormalities: high mitral A-wave velocities and lower E/A ratio, lower DTI lateral peak E-wave velocities [70].

Another predictor of LV dysfunction in DMD patients is the myocardial performance index (MPI) gained by using pulse-wave Doppler and Doppler tissue imaging. Based on the intraclass coefficient correlation, MPI obtained with Doppler tissue imaging was more reproducible.

STE is a modern technique capable to determine subclinical LV dysfunction before the overt LV EF reduction, that is recently frequently used in DMD patients. The myocardial strain is irregular in almost 50% of DMD patients, showing lower GLS values compared to the control group notwithstanding a normal LV EF [71, 72]. Furthermore, a reduction of 0.34%/year of GLS value in DMD patients according to age has been described [73]. In this study, in patients with DMD were observed differences in longitudinal (3.6%), radial (9%), and circumferential (3.8%) strains compared to healthy controls, with significantly lower values in the inferolateral and anterolateral mid-basal segments [73].

Another retrospective studies previously described circumferential and longitudinal strains in DMD patients with a greater difference for these indicators [67, 70]. However, STE analysis is often restricted in DMD because the echocardiographic picture quality is low in these patients due to chest malformations, lung hyperinflation, and limited mobility and decays by 2.5% for each 1-year in plus in age [66]. There was a suboptimal echocardiographic quality, defined as more than 30% of segments incompletely visualized, observed in 50% of 13-year-old DMD patients and 78% of 15-year-old patients [66].

Surely, LV EF, obtained by echocardiography, has been demonstrated to associate with CMR, while 2-D FS and 5/6 area length LV EF correlated strongly with CMR LV EF [26, 67].

Right ventricular (RV) function is frequently protected

in DMD patients, accompanying by LV dysfunction, presumably because of the decreased afterload of respiratory changes. In Mehmood et al. study normal RV values were reported in subjects with severe LV dysfunction, and only in few cases there have been described advanced RV dysfunction [74].

Therapeutic management for DCM-DMD

Usually, HF changes the definition to the manifestation of clinical symptoms. Most DMD patients are asymptomatic for a long time of their life, so identifying predictors of HF is essential to maintain these patients. Ventricular dysfunction based on the EF measurement helps to provide therapy. DMD DCM can be classified as normal LV EF (≥50%), mid-range (40-49%), and reduced LV EF (<40). In the following section, all cardiovascular drug therapies are described according to LV EF [75].

Early DCM (LVEF≥50%)

The great purpose is to prevent the ventricular dysfunction incipience at this stage of the disease. Because of specific therapy absence for HF in DMD, 2018 DMD Care Guidelines recommend traditional first-line HF therapy with angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) [16].

In 2005, Duboc D. reported results of five-year study for the prophylactic use of perindopril in DMD patients. This research had to estimate the perindopril effect on LV dysfunction history. In this study, 57 children aged 9.5 to 13 years with a normal cardiac test and LV EF of more than 55%, were randomized to perindopril 2–4 mg versus the placebo group. The chi-squared analysis revealed a significant advantage for patients treated to prevent the progression of DCM, described as the decrease of LV EF under 45%. After this study, ACEi has been initiated to be prescribed in prophylactic scopes [76].

DMD DCM with Mid-Range Reduction of LV EF (40-49%)

Several kinds of research have been labeled for DMD patients with moderate systolic LV dysfunction and showed some beneficial effects to preserve its appearance. Current guidelines recommend the use of conventional HF medication in case of disease progression. In 2013, Allen H. compared the outcomes of lisinopril with losartan in a randomized, double-blind, controlled trial of 22 DMD patients, that showed no difference between lisinopril and losartan in controlling ventricular function [77].

The cardioprotective impact of eplerenone in combination with ACE-I or ARB was assessed by CMR after 12 months in 42 DMD patients. In this multicenter, randomized, placebo-controlled trial, Raman S. et al. revealed that eplerenone decreased the decline of magnetic resonance assessed LV circumferential strain and LV EF at 12 months when matched to the placebo group [78]. Also, Raman S. et al. showed that early MRA therapy is effective and safe in a genetic disease with high cardiomyopathy risk [79].

Accordingly, at the ambulatory stage of the disease, before any clinical overt DCM, the preventive use of perindopril for cardioprotection is started extensively in the clinical practice and endorsed by current indication although biological consequences are still unclear. When the DCM is detectable even in case of a mild reduction of EF (>45% LVEF), fosinopril or losartan with the combination of MRA can increase ventricular function.

Also, beta blockers (BB) have been tested. In 22 patients carvedilol was administered and progressively increased over 8 weeks. This therapy modestly improved cardiac CMR-derived measured EF (41% +/− 8.3% to 43% +/− 8%; $p < 0.02$), as well as the MPI (0.55 +/− 0.18 to 0.42 +/− 0.15; $p < 0.01$) and the mean rate of pressure rise (dP/dt) during isovolumetric contraction (804 +/− 216 to 951 +/− 282 mmHg/s; $p < 0.05$) [80].

Patients with Severe Ventricular Dysfunction (<40%)

The therapeutic approach for patients with significant DCM has been studied less profoundly and contemporary guidelines recommend all drugs used for HF treatment [12, 15, 81].

Although in adult HF, the use of BBs is obligatory in declining of ventricular function, the same evidence in children is absent. Last years, some retrospective and non-randomized prospective studies have confirmed the beneficial effect of BB therapy in patients with DMD [51, 79, 82-84], while in some others this positive effect was not detected [85, 86]. Although most of the studies are retrospective and included different ages, BB in addition to ACEi demonstrated to improve 5-year and 7-year survival rates [84], and also ventricular function [82]. These contradictory conclusions have provided to the variable and frequently insufficient beginning of BB in DMD. However, BB are usually combined with ACEi/ARB when a sufficient change in heart function is not assessed with basic therapy.

Moreover, in DMD, this therapy is often designated for the appearance of autonomic dysfunction and the following predilection to arrhythmias [87]. In the contemporary literature the most frequently used drugs are: carvedilol (0.01–0.02 mg/kg) administered twice daily and slowly increased to a dose of 0.5–1 mg/kg [51,80,82,83,85], metoprolol (1 to 2 mg/kg/day) [51, 86] and bisoprolol (3–4 mg per day) [84].

In some studies, combined therapy with ACEi/BBs has demonstrated to be better to single ACEi [80, 82] in the prevention of major cardiac emergencies [83] and long-term survival [84].

End-Stage of DMD DCM

It was recently demonstrated the utility of the HR reduction approach achieved with BBs and ivabradine (2.5 mg twice daily increasing until 15 mg daily every two weeks when HR was still above 70 bpm and LVEF < 40%) in the decrease of the long-term trend of acute adverse effects in DMD patients with advanced heart implication [88]. Previously, ivabradine demonstrated the effectiveness in HR reducing and LV EF improving in a multicenter, randomized, placebo-controlled trial in children with DCM and HF symptoms [89].MRAs, spironolactone, and eplerenone are recommended in all symptomatic patients (despite treatment with an ACE-I and BB) with HF and LV EF ≤ 35%, to decrease death and hospitalization conform to Ameri-

can and European Guidelines for the management of HF in adults [75, 90].

Shortly a new mineralocorticoid receptor antagonist (MRA) called vamorolone, will be able to imitate the anti-inflammatory impact of glucocorticoids, presumably could be a real alternative to both "old MRAs" and "glucocorticoids" in the DMD therapy [91]. To date, there are no clinical studies about the use of MRAs in an advanced stage of DCM in DMD patients. Despite this, eplerenone or spironolactone are used in these patients, at the cardiologist's decision, in combination therapy with ACEi and BB, till they do not manifest hyperkalemia or renal insufficiency.

Sacubitril/valsartan, the first-in-class angiotensin receptor neprilysin inhibitor (ARNI) has recently been approved by the Food and Drugs Administration for the treatment of children with symptomatic HF and systemic LV systolic dysfunction, that was based on the reduction in the NT-proBNP levels in sacubitril/valsartan groups compared to enalapril one after 12 weeks of treatment in PANORAMA-HF trial [92].

Advanced Cardiac Therapies

Heart Transplant and Mechanical Assist Device

A potential therapy for end-stage HF in these patients is the use of a left ventricle assist device (LVAD) as destination therapy (DT) [93, 94]. LVAD treatment significantly created a reverse ventricular improvement within various mechanisms: reducing ventricular volume, LV mass, hypertrophy, and improving its function [95-101]. The use of mechanical circulatory support in DMD was described in several case reports and small series [102-107*DMD Target Therapy*

Glucocorticoid therapy has been the standard for patients with DMD. Deflazacort and prednisone are the most recommended steroids. Their introduction changed the natural history of the disease, increasing the ambulation period, preventing cardiorespiratory insufficiency, and enhancing life-expectancy [16, 44].

The curative strategies for DMD have focused on replacing dystrophin expression or moderating the processes of dystrophin deficiency.

The strategies embraced for dystrophin protein restoration are the following: nonsense readthrough, antisense oligonucleotides for exon skipping, and gene therapy. Inflammation inhibiting, reducing fibrosis, promoting muscle regeneration, and mitochondrial function facilitating are used to mitigate the dystrophic processes.

This translational investigation has managed the acceptance of the first target therapies for DMD. Ataluren (Translarna™, PTC Therapy) is the first licensed drug for DMD in Europe. Ataluren is an oral molecule that connects ribosomal RNA subunits and lets ribosomal read through of mRNA including a premature stop codon. It is recommended for the therapy of DMD with a nonsense mutation in the dystrophin gene.

Recent FDA approved AONs targeting exon 51 (eteplirsen) and 53 (golodirsen) for DMD treatment [87].

Conclusions

Information about dystrophinopathies including DMD has been rapidly increasing since the initial study by Guillaume Duchenne. It is necessary to recognize that these patients, mostly teenagers and young people, need to be sufficiently managed with the best perspectives, and not with conformism and fatality, which in general quickly condemn patients with rare diseases, particularly with poor life-expectancy prognosis. In a careful but positive way, cardiologists should be mindful of recent studies to implement the best available follow-up and management.

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Authors' contribution
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Funding
The journal publication fee was covered by Institute of Mother and Child. The study was supported by *Nicolae Testemitanu* State University of Medicine and Pharmacy as a PhD program. The authors are independent and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate
No approval was required for this review study.

Conflict of Interests
The authors have no conflict of interests to declare.