AHA SCIENTIFIC STATEMENT

Management of Cardiac Involvement Associated With Neuromuscular Diseases

A Scientific Statement From the American Heart Association

ABSTRACT: For many neuromuscular diseases (NMDs), cardiac disease represents a major cause of morbidity and mortality. The management of cardiac disease in NMDs is made challenging by the broad clinical heterogeneity that exists among many NMDs and by limited knowledge about disease-specific cardiovascular pathogenesis and course-modifying interventions. The overlay of compromise in peripheral muscle function and other organ systems, such as the lungs, also makes the simple application of endorsed adult or pediatric heart failure guidelines to the NMD population problematic. In this statement, we provide background on several NMDs in which there is cardiac involvement, highlighting unique features of NMD-associated myocardial disease that require clinicians to tailor their approach to prevention and treatment of heart failure. Undoubtedly, further investigations are required to best inform future guidelines on NMD-specific cardiovascular health risks, treatments, and outcomes.

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Neuromuscular diseases (NMDs) encompass a broad spectrum of diagnoses with overlapping but distinct phenotypes. Common to many NMDs is cardiac involvement. Although the past 3 decades have seen marked advances in our understanding of many NMDs, significant gaps in knowledge remain on how best to approach cardiac care in these patients. For example, survival in Duchenne muscular dystrophy (DMD) has been extended through the use of glucocorticoid use and respiratory support, yet cardiac complications remain a significant cause of morbidity and mortality.[1–3] To achieve further gains in care, we will need to improve our understanding of the pathophysiologies driving cardiac involvement in NMDs and advance treatments aimed at preventing the progression of heart failure (HF) and sudden death in NMDs. The recently published findings of an expert working group on cardiac involvement in DMD, which outlined key gaps in knowledge and made specific recommendations aimed at improving diagnosis and management, are a step toward this goal.[4]

In this statement, we include a comprehensive overview of the major categories of NMDs with cardiac involvement. For each, a brief background of the gene defect(s), common clinical manifestations (particularly cardiac findings), and current therapies is summarized. Gaps in knowledge are highlighted, and where possible, clinical treatment suggestions are made by the expert writing group appointed by the American Heart Association to review the available literature. Selection of the writing group was performed in accordance with the American Heart Association's conflict-of-interest management policy. Participants volunteered to write sections relevant to their expertise and experience. Writing group members

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

conducted a general search of the literature, restricted to human subjects research published between 1980 and 2016. Drafts of each section were written and sent to the chair of the writing group for incorporation into a single document, which was then edited. The edited document was discussed electronically and by conference call among the participants as a group. On the basis of these discussions, the sections were then edited, and a final version of the document was produced. Recommendations were generated from this process and then assigned a class of recommendation and level of evidence (Table 1). The final document was submitted for independent peer review and has been approved for publication by the American Heart Association Council on Cardiovascular Disease in the Young.

OVERVIEW OF NMDs WITH CARDIAC INVOLVEMENT

Inherited NMDs are genetic disorders typically caused by a mutation in a single gene that affects striated muscle and results in progressive weakness in affected individuals from degenerative muscle pathology. In addition to skeletal muscle, cardiac muscle can also be affected, with some variability dependent on the ge-

netic basis of the NMD phenotype. As shown in Table 2, inheritance can be X-linked, autosomal dominant, or autosomal recessive. Of note, genotypic identification of NMD pathogeneses is a relatively recent phenomenon, and genotype-phenotype correlations continue to evolve. This broad diversity of NMD genetic causes translates into many different sites of involvement in affected myocytes (Figure).

Table 2. Characteristics of NMDs With Cardiac Involvement Addressed in This Statement

Condition	Gene Locus	Gene Product	Heritance	Cardiac Features		
				Cardiomyopathy	Arrhythmia	Conduction
X-linked recessive muscular dystrophies						
Duchenne	Xp21	Dystrophin	XLR	Common (DCM)	Common (late)	Rare (late)
Becker	Xp21	Dystrophin	XLR	Common	Common	Rare (late)
Emery-Dreifuss	Xq28	Emerin	XLR	Rare	Common	Common (SD)
Limb-girdle muscular dystrophies						
LGMD1B	1q11–q21	Lamin A and C	AD	Common (DCM)	Common (AT, VT)	Common (SD)
LGMD1C	3p25	Caveolin-3	AD	Rare (DCM)	Not reported	Rare (AVB)
LGMD1E	7q36	DNAJB6 (co-chaperone)	AD	Rare	Rare	Rare
LGMD2B	2p13	Dysferlin	AR	Rare (DCM)	Not reported	Not reported
LGMD2C	13q12	γ-Sarcoglycan	AR	Common (DCM)	Rare	Rare
LGMD2D	17q12–q21	α-Sarcoglycan	AR	Common (DCM)	Rare	Rare
LGMD2E	4q12	β-Sarcoglycan	AR	Common (DCM)	Common	Common
LGMD2F	5q33–q34	δ-Sarcoglycan	AR	Rare	Rare	Rare
LGMD2I	19q13.3	Fukutin-related protein	AR	Common (DCM)	Rare	Rare
Associated with mitochondrial dysfunction						
Barth syndrome	Xq28	Tafazzin	XLR	Common (LVNC, DCM, HCM)	Occasional	None
Friedreich ataxia	9q21.11	Frataxin	AR	Common (HCM)	Common (late)	Rare
Myotonic dystrophies						
Myotonic dystrophy (DM) 1	19q13	Myotonin-protein kinase	AD	Occasional (DCM, HCM)	Common (AFL/AF, VT)	Common (SD)
Myotonic dystrophy (DM) 2	3q21	Zinc finger protein 9	AD	Rare in childhood	Rare in childhood	Rare in childhood
Congenital myopathies						
Central core disease	19q13.2	Ryanodine receptor	AD/AR	Rare (DCM)	Not reported	Not reported
Nemaline myopathy	1q21, 2q21–q22, 1q42.13, 19q13.4	α-Tropomyosin, nebulin, skeletal muscle α-actin, troponin T	AR/AD	DCM, HCM	Rare (long QT)	Common (mild)
Multiminicore disease	19q13.2, 1p36.13	Ryanodine receptor, selenoprotein N1	AR	Rare (HCM, RCM)	Unknown	Unknown
Centronuclear myopathy	19p13.2, 2q14, 2q31	Dynamin 2, bridging integrator 1, titin	AD/AR	Rare (DCM)	Rare	Rare
Myotubular myopathy	Xq28	Myotubularin	XLR	Not reported	Not reported	Not reported
Myosin storage myopathy	14q12	β-Myosin heavy chain	AD	Not reported	Not reported	Not reported
Congenital fiber type disproportion	1q21.2, 19q13.2, 1q42.13	α-Tropomyosin, ryanodine receptor, skeletal muscle α-actin	AR/AD	Rare (DCM)	Not reported	Not reported
Myofibrillar myopathies						
	2q35, 5q31, 10q22.3–q23.2, 11q23.1, 7q32–q35, 10q25.2–q26.2, Xq26	Desmin, myotilin, LIM domain binding protein 3, crystallin alpha B, filamin C gamma, BCL2-associated athanogene 3, four-and-a-half LIM domains 1	AD	Common	Rare (late; AF)	Rare (AVB)

AD indicates autosomal dominant; AF, atrial fibrillation; AFL, atrial flutter; AR, autosomal recessive; AT, atrial tachycardia; AVB, atrioventricular block; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LGMD, limb-girdle muscular dystrophy; LVNC, left ventricular noncompaction; RCM, restrictive cardiomyopathy; SD, sudden death; VT, ventricular tachycardia; and XLR, X-linked recessive.

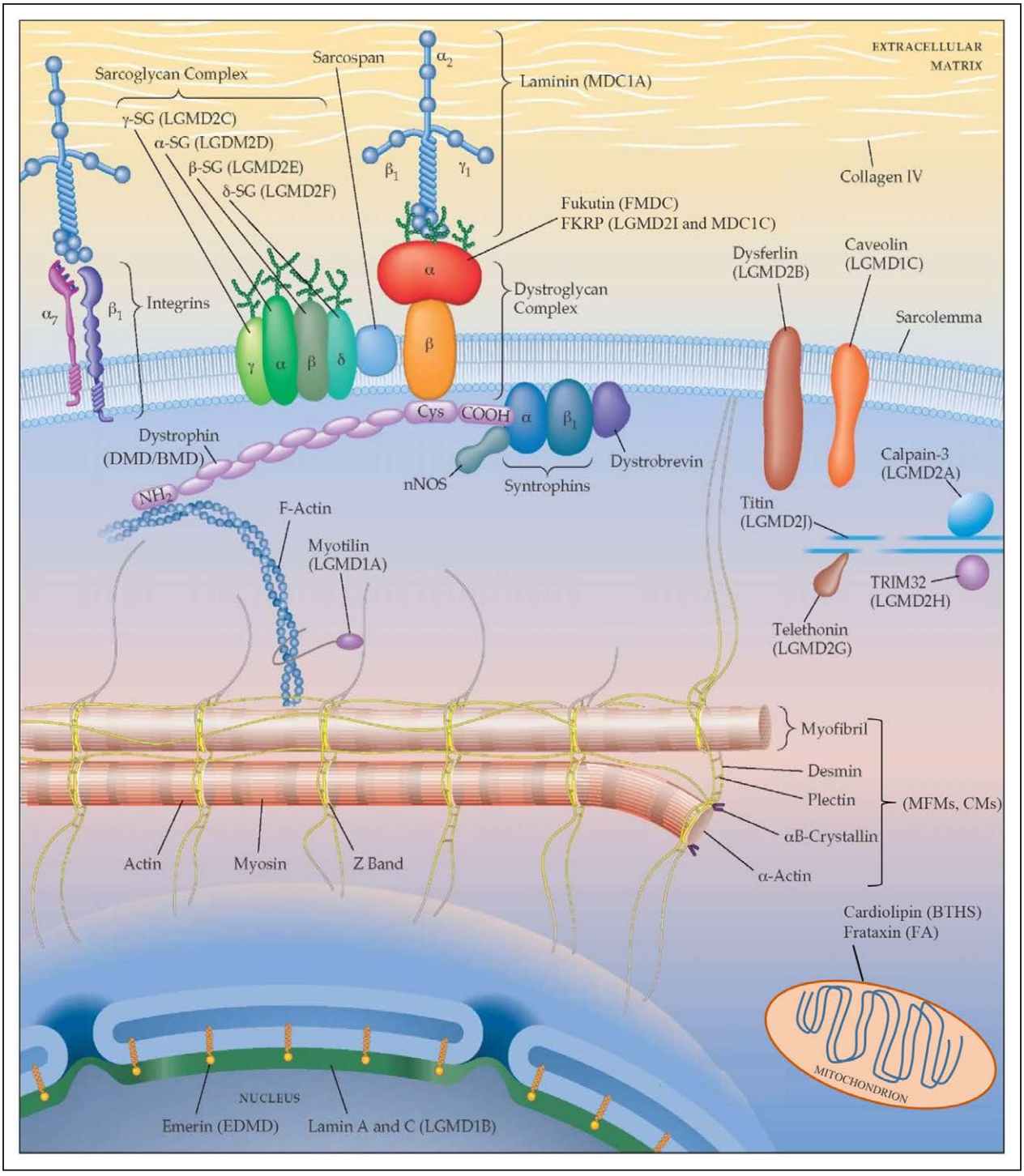

Figure. Proteins implicated in NMDs associated with cardiac involvement.
BMD indicates Becker muscular dystrophy; BTHS, Barth syndrome; CMs, congenital myopathies; Cys, cysteine; DMD, Duchenne muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; FA, Friedrich ataxia; FKRP, fukutin-related protein; FMDC, Fukuyama congenital muscular dystrophy; LGMD, limb-girdle muscular dystrophy; MDC, congenital muscular dystrophy; MFMs, myofibrillar myopathies; NMDs, neuromuscular diseases; and nNOS, neuronal nitric oxide synthase. Modified figure used courtesy of Dr Marinos Dalakas.

Clinically relevant cardiac involvement in NMDs most commonly falls into 1 of 2 major categories: (1) cardiomyopathy and (2) conduction defects with arrhythmias. The severity and onset of cardiac complications vary significantly across classes of NMDs. Most forms of cardiac involvement are detected from childhood to the second decade of life (eg, DMD, myotonic dystrophy [DM], Friedreich ataxia [FA], Emery-Dreifuss muscular dystrophy

[EDMD], Barth syndrome [BTHS]), but others can remain asymptomatic until later in life (Becker muscular dystrophy [BMD], some forms of congenital myopathy [CM], and myofibrillar myopathy [MFM]). In some cases, cardiac involvement is more severe when neuromuscular symptoms appear in childhood or show a rapid progression during infancy; however, in most cases, the progression and onset of cardiac involvement are dissociated from or occur late after the development of skeletal myopathy, and poor correlation exists between genotype and phenotypes at the cardiac and skeletal muscle levels.[5]

The importance of genetic testing in the diagnosis of NMDs must be noted. Because there can be significant phenotypic overlap among NMDs at initial presentation,[6] genetic testing is crucial to the diagnostic workup of NMDs, commonly allowing for a definitive diagnosis.[6,7] Although typical disease inheritance patterns and genetic pathogeneses are shown in Table 2, both spontaneous mutations resulting in disease and phenotypic variability within family members who share the same underlying mutation can sometimes cloud diagnosis. Knowledge of the specific underlying disease process provides vital information about clinical expectations and genetic counseling, as well as prenatal diagnosis. From the cardiovascular perspective, having a precise genetic diagnosis is important because of the heterogeneity in cardiovascular manifestations among NMDs. Some NMDs increase the risk of cardiomyopathy and HF (eg, DMD, BMD, FA), others elevate the risk of arrhythmia and sudden death (eg, EDMD, limb-girdle muscular dystrophy [LGMD]1B, and DM1), others increase risk of both (eg, BTHS, MFM), and still others do not involve the heart (eg, LGMD1D, oculopharyngeal muscular dystrophy). Thus, although at present a definitive diagnosis determines the timing and modes of cardiovascular assessment and follow-up, it is expected that definitive genetic diagnosis will eventually allow not only for NMD-specific therapies but also for mutation-specific therapies.

DMD and BMD

The most common NMDs affect the dystrophin gene found on the short arm of the X chromosome. These "dystrophinopathies" comprise both DMD and BMD. The incidence of DMD was determined to be 1 in 3600 to 1 in 9300 male births by a recent worldwide systemic review.[8] DMD is the more severe phenotype, presenting with weakness in the early years and progressing to loss of the ability to walk independently, most commonly during the second decade. This phenotype has been influenced by treatment with glucocorticoids, which was shown in a randomized clinical trial to prolong the period of independent ambulation by 3 years.[9] BMD is a milder and more variable phenotype, and patients with BMD are not typically treated with glucocorticoids.[10]

Respiratory insufficiency invariably develops in patients with DMD, usually during the second decade of life. The lung disease is restrictive, because of weakness of the muscles required for respiration. As the disease progresses, noninvasive ventilator support is required while sleeping. Some patients maintain respiratory function in the later stages of the disease with invasive mechanical ventilation through a tracheostomy or continual support using other noninvasive methods, such as mouthpiece ventilation.

DMD most commonly results from multiple exon deletions in the dystrophin gene that disrupt the reading frame and thus preclude translation of a full-length dystrophin protein. The truncated protein is not stable and degrades, resulting in nearly complete absence of dystrophin protein. In contrast, the most common mutation that causes BMD is a multiple-exon deletion in the dystrophin gene that does not disrupt the reading frame. This type of deletion results in dystrophin protein that has an internal deletion with retention of the amino and carboxy termini that localize the protein to the cytoplasmic face of the sarcolemma, thus providing a partially functional protein. Smaller gene deletions, gene duplications, and point mutations account for a smaller fraction of both DMD and BMD.[10]

The most common cardiac involvement in DMD and BMD is dilated cardiomyopathy, which can be variable in age of onset and severity. Compared to other causes of dilated cardiomyopathy, DMD and BMD have less ventricular dilation early in the course of disease, simply beginning with dysfunction without dilation.[11–13] For patients with DMD, cardiac disease is the primary cause of mortality in >20%,[14] and previous observational studies have shown that increasing cardiac dysfunction is correlated with increasing age and severity of skeletal muscle disease.[15,16] Recent studies have suggested that the average age for development of abnormal left ventricular ejection fraction (LVEF) is 14.3 years.[13,17] Because of limitations of movement caused by skeletal muscle disease, early signs of cardiac failure may not appear clinically. Decreased cardiac function or left ventricular (LV) dilation might only be detected by echocardiogram or other cardiac imaging.[18] For BMD, only a small proportion of subjects <16 years of age have symptomatic involvement.[13] Although this risk increases with age, with up to 70% developing symptomatic HF by age 40,[19] disease progression is much less predictable than for DMD.[20] Because of the underlying pathogenesis (myocyte disruption attributable to abnormal dystrophin protein), conduction system involvement is not a feature of DMD and BMD as it is with many other NMDs. Although the risk of tachyarrhythmia in DMD and BMD generally increases with the severity of ventricular dysfunction, tachyarrhythmias, including supraventricular tachycardia, can also occur with normal ejection fraction (EF).[21–23]

Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy is a descriptive term for a group of muscular dystrophies that are distinct from the more common X-linked dystrophinopathies. LGMDs are classified by autosomal dominant (LGMD1) or autosomal recessive (LGMD2) inheritance,[24] with mutations at >50 loci reported.[25] Prevalence estimates for LGMD are 1 in 14 500 to 1 in 123 000.[26,27]

LGMD2 generally presents during childhood or adolescence as a progressive skeletal myopathy that results in severe disability, with phenotypic overlaps with DMD and BMD.[28] The distribution and pattern of weakness at onset most often affect the pelvic or shoulder girdle musculature or both. Table 2 shows a subset of LGMD2 disorders, each of which can have a cardiac phenotype.[28,29] Disruption of the sarcolemmal membrane cytoskeleton is a common feature of LGMD2C, 2D, 2E, and 2F, also known as sarcoglycan-deficient muscular dystrophies. Age of onset is from 2 to 15 years. Weakness involves proximal more than distal musculature, although progression is variable. There is a broad range of phenotypic variation that can include calf pseudohypertrophy, scapular winging, progressive contractures, and scoliosis.[30] Loss of ambulation varies from 10 years to young adulthood.

LGMD2I is caused by pathogenic mutations in the gene for FKRP (fukutin-related protein), which is involved in the glycosylation of cell surface molecules in muscle fibers.[31] The majority of LGMD2I patients carry a common C826A missense mutation.[32–34] LGMD2I has a relatively mild and variable course, with the age of onset varying from the first to the fifth decade of life and usually having slow progression. Cardiomyopathy without skeletal muscle involvement has been reported.[35]

There is broad clinical heterogeneity among the various LGMDs. Therefore, accurate diagnosis is important to ensure appropriate cardiac evaluation and follow-up.[6] Cardiac involvement is very common in lamin A/C and sarcoglycan disease, whereas significant cardiac involvement is infrequent in calpain and dysferlin disease.[36] Cardiac complications include atrial and ventricular arrhythmias, various degrees of heart block, and cardiomyopathy. Of note, both dilated and hypertrophic cardiomyopathies have been described.[24,37] Respiratory muscle weakness also varies in severity but complicates the evaluation and management.[36]

Emery-Dreifuss Muscular Dystrophy

EDMD is another nondystrophinopathy with associated cardiac involvement characterized by early-onset joint contractures (elbows, ankles, and cervical spine), slowly progressive muscle weakness, and cardiac conduction defects that increase the risk of sudden death. EDMD has significant clinical variability and is caused by mutations in genes that code for nuclear envelope proteins. X-linked EDMD, the prevalence of which is ≈1 in 100 000, is caused by mutations in *EMD* (encoding emerin) or *FHL1* (encoding FHL1).[38,39] Autosomal dominant and autosomal recessive forms are caused by mutations in *LMNA* (encoding lamins A and C).[40,41] Mutations in the same genes that cause EDMD can also cause an LGMD phenotype. EDMD is distinctive for its association with progressive abnormalities in the cardiac conduction system that can result in heart block and sudden death.[21,42] On autopsy studies of individuals with X-linked EDMD, gradual replacement of myocardium by fibrous and adipose tissue, starting in the atria and often involving the atrioventricular node and eventually the ventricles, has been observed and is consistent with atrial arrhythmias (including bradycardia), heart block, and progressive ventricular dilatation and systolic dysfunction observed clinically in EDMD.[43]

Myofibrillar Myopathy

MFM is a relatively newer morphological classification that refers to a subgroup of rare, inherited or sporadic, progressive NMDs defined by the common appearance of foci of myofibril disruption that begins at the sarcomeric Z-disk. Generally, myofibril dissolution is followed by abnormal accumulation of myofibrillar degradation products and ectopic expression and aggregation of multiple proteins in affected muscle fibers.[44] Diagnosis of MFM is traditionally based on common histological findings, although no morphological feature consistently or reliably predicts a specific gene mutation or clinical outcome. Six genes have been traditionally associated with MFM, and mutations in these genes account for ≈50% of all cases of MFM: *DES* (encoding desmin), *MYOT* (encoding myotilin), *LDB3*/*ZASP* (encoding LIM domain binding 3), *CRYAB* (encoding crystallin alpha B), *FLNC* (encoding filamin C, gamma) and *BAG3* (encoding BCL2-associated athanogene 3). Recently, mutations in *FHL1* (encoding four-and-a-half LIM domains 1), *DNAJB6* (encoding a DNAJ protein family member), and *TTN* (encoding titin) have also been linked to MFM, and the list of genes causing MFM will likely continue to grow.[45] MFM is most commonly inherited in an autosomal dominant manner, with notable exceptions for *FHL1* mutations (X-linked) and *CRYAB* (autosomal recessive).[45] The prevalence of MFM is currently undetermined.

Clinically, MFM develops later in life, with symptoms beginning at 30 to 50 years of age (range 7–77 years). It is characterized by slowly progressive muscle weakness, from distal to proximal lower extremities, with eventual involvement of upper extremities, trunk, and facial and respiratory muscles. Peripheral neuropathy and cardio-

myopathy are associated features in 15% to 30% of patients.[46,47] Childhood onset has been described for mutations in *DES*, *CRYAB*, *BAG3*, and *FHL1*. It is a rapidly progressive disease, leading to the development of debilitating contractures, severe cardiomyopathy (sometimes preceding skeletal muscle involvement), and cardiorespiratory failure. Consistently, cardiac involvement is more prevalent in mutations that cause childhood-onset MFM and has been reported as dilated (*DES*, *FHL1*), hypertrophic (*CRYAB*, *BAG3*, *FHL1*), or restrictive (*BAG3*, *DES*) cardiomyopathy. Associated features include sinus node dysfunction, atrioventricular block, supraventricular and ventricular tachycardias, HF, and sudden death.[46,48–53]

Barth Syndrome

BTHS is a rare X-linked, recessive mitochondrial myopathy that was initially described in 1983 among a Dutch pedigree of male infants with dilated cardiomyopathy, neutropenia, and skeletal myopathy.[54] As of 2013, 151 cases had been described worldwide with an estimated incidence between 1 in 140 000 and 1 in 670 000 births.[55–57] Increasing identification of LV noncompaction (LVNC) because of improved imaging and awareness could uncover additional cases of BTHS.[58,59] BTHS is caused by a mutation in the *TAZ* gene on Xq28 responsible for encoding tafazzin protein. This protein is involved in cardiolipin remodeling, an important component of the mitochondrial inner membrane necessary for proper function of the mitochondrial respiratory chain.[55] At present, genotype does not predict phenotypic course.

Noncardiac clinical manifestations of BTHS include neutropenia, skeletal myopathy, prepubertal growth restriction, cognitive impairments, and typical facial features. Neutropenia is recognized in more than two-thirds of cases and can be associated with mouth ulcers (60%), pneumonia (28%), or bacteremia/sepsis (10%), although severity varies widely.[60] Skeletal myopathies are nonprogressive and affect proximal muscles, leading to motor delays at a young age. Prepubertal height and weight are proportionally delayed; however, many experience postpubertal catch-up growth.[61] Minor learning disabilities are common, particularly within mathematics, visual-spatial skills, and speech development.[60,62] Typical facial features include a round face, full cheeks, prominent pointed chin, large ears, and deep-set eyes and are most prominent in infancy.[57]

Cardiac disease is the most common presenting feature of BTHS, with evidence of cardiomyopathy before age 5 years and often (>70%) within the first year of life.[60] Cardiomyopathy manifests as ventricular dilation with or without features of LVNC, endocardial fibroelastosis, or LV hypertrophy, often as a mixed hypertrophic and dilated phenotype.[56,60] Clinical course is highlighted by an undulating phenotype with evolution of cardiomyopathy subtype over time. It is hypothesized that remodeling occurs with evolution from hypertrophy to dilation during early childhood, followed by improvement during the toddler years and subsequent progressive late dilation/decline in a subset of the population.[57] This undulating phenotype has been described in patients with LVNC.[63] It is unclear whether LVNC is solely responsible for this observation within BTHS.

In addition to cardiomyopathy, boys with BTHS are at risk for tachyarrhythmia. Electrocardiographic abnormalities early in life include repolarization abnormalities, such as ST flattening and T-wave inversions or prolonged corrected QT interval.[55] Supraventricular and ventricular tachycardia resulting in sudden death have been reported in adolescents and young adults with only mildly decreased LVEF.[64] A history of syncope or orthostatic symptoms, as well as a family history of sudden death, may be predisposing factors.[64]

Friedreich Ataxia

FA is an inherited neuromuscular disorder that arises from a triplet repeat expansion mutation in the first intron of the gene encoding frataxin (*FXN*, also known as *X25*).[65] In contrast with most other triplet repeat expansion disorders, FA is inherited in an autosomal recessive manner. Its prevalence is ≈1 in 50 000, with a carrier rate of 1 in 60 to 1 in 100.[66] FA affects men and women equally. Approximately 2% to 5% of affected individuals have a different type of mutation in 1 copy of *FXN* instead of an expansion of the GAA repeat in intron 1.[67,68] The normal size for this GAA repeat is ≤30 copies, and affected individuals typically have >70 triplets on each copy of this gene. An intermediate size (30–70) is classified as premutation, which is more susceptible to expansion in future generations.

Cardiac disease is the most life-threatening manifestation of FA.[69] Additional systemic features include progressive cerebellar dysfunction, ataxia, scoliosis, diabetes mellitus, impaired speech, and loss of vision and hearing. The spectrum of phenotypic features of FA fits best with a mitochondrial disorder, although frataxin is encoded by nuclear DNA. Frataxin plays an essential role in the synthesis of Fe-S (iron-sulfur) cluster proteins involved in the regulation of mitochondrial iron content.[70] In a conditional mouse model with complete frataxin deficiency in cardiac and skeletal muscle, the activities and levels of mitochondrial Fe-S proteins are much lower than in age-matched controls.[71] Consequently, mitochondrial iron levels are increased, with associated mitochondrial dysfunction and severe oxidative stress despite normal levels of iron in blood.

Typical age of FA onset is 5 to 15 years, although later onset also occurs. The severity of most phenotypic

manifestations correlates loosely with the size of the smaller of the 2 expanded GAA repeats.[72] Additional variation in the age of onset and progression of disease could be attributable to other genetic and environmental factors.[73] Cardiac manifestations consist of LV hypertrophy with fibrosis and scarring, arrhythmias, and progressive HF. Cardiac dysfunction is the most frequent cause of death in FA.[74]

Myotonic Dystrophy

Myotonic dystrophy, or *dystrophia myotonica*, is part of a heterogeneous group of inherited NMDs that, like FA, result from genetic expansion and instability of simple nucleotide tandem repeats. There are 2 recognized forms of DM: myotonic dystrophy type 1 (DM1), also known as Steinert disease, and myotonic dystrophy type 2 (DM2), also known as proximal myotonic myopathy (PROMM) or Ricker disease.[75] Both DM types are inherited in an autosomal dominant manner and share a common core of clinical manifestations. It is probable that pathology is associated with intracellular disruption of the RNA transcript–processing machinery in affected cells.[76–78] DM prevalence is estimated at ≈1 in 8000 worldwide, but occurrence of the 2 types of DM varies widely among ethnic groups.[79,80]

DM1 is caused by expansion of an unstable CTG trinucleotide repeat in the 3′ untranslated region of the *DMPK* gene. DM1 can be progressive or congenital, manifesting in children and adults with muscle weakness and myotonia and in neonates with generalized hypotonia.[75,81] Diagnosis is confirmed by genetic testing, with affected individuals having >35 trinucleotide repeats. In general, longer repeat expansion correlates with higher penetrance, earlier onset, and increased severity of disease.[81] Clinically, DM1 is characterized by progressive development of facial, neck, and distal limb muscle weakness and myotonia. Other degenerative symptoms include cataracts, neurological/neuropsychiatric deficits, and endocrine/metabolic abnormalities.[82–84] There is a tendency for successive generations to show symptoms at an earlier age or with more severe manifestations (ie, anticipation).[75,85]

Similar to DM1, DM2 is a multisystem disease characterized primarily by myotonia and muscle wasting.[80,86] DM2 is caused by expansion of a CCTG repeat in intron 1 of *CNBP* (encoding CCHC-type zinc finger, nucleic acid binding protein). The number of repeats in DM2 ranges from ≈75 to 11 000. DM2 shows a higher degree of variability in clinical manifestations and age of onset (20–70 years), but clinical course and life expectancy are generally more favorable than DM1.[80,81,86] There is no genetic anticipation and no congenital form of DM2.[86,87]

Cardiac manifestations are present in ≈80% of DM1 patients, and the risk of developing cardiac disease is 10- to 20-fold higher in younger patients (2–30 years old).[88] Dilated cardiomyopathy has been reported, but progressive atrioventricular or intraventricular conduction defects and tachyarrhythmias (ventricular and supraventricular) are the most life-threatening forms of cardiac complications.[89–91] In older patients, age-related cardiovascular diseases such as valvulopathy and coronary artery disease may also be observed.[92] Respiratory complications and cardiac arrhythmias are the most frequent primary causes of death in DM1.[93,94]

In patients with DM2, cardiac problems appear to be less severe or frequent (10%–20%). Conduction defects are normally limited to first-degree atrioventricular and bundle-branch block; however, sudden death and severe cardiac arrhythmias have been described in a small number of patients.[95] Dilated cardiomyopathy is uncommon.[80,81,86]

Congenital Myopathy

Historically, CMs represent a heterogeneous group of muscular disorders that have been defined by the presence of specific morphological abnormalities of muscle fiber architecture on skeletal muscle biopsy samples, including rods (ie, nemaline myopathies), cores (central core and multiminicore diseases), central nuclei (centronuclear-myotubular myopathy), hyaline bodies (myosin storage myopathy), and selective atrophy of type I fibers (congenital fiber type disproportion).[96,97] To date, these structural abnormalities have been linked to >15 different genes, most of which code for sarcomeric or intracellular proteins involved in myofiber integrity.[98] Genotype-to-phenotype correlations are not straightforward, with many common pathological features being linked to mutations in different genes and mutations in the same gene causing different muscle pathologies.[97] Prevalence is estimated to be 1 in 26 000 to 28 000, with mutations in *RYR1* (encoding ryanodine receptor 1) being the most prevalent (≈1 in 90 000).[99]

Clinically, CMs have been defined recently as "a group of genetic muscle disorders characterized by hypotonia and weakness, usually from birth, and a static or slowly progressive clinical course."[97] Although it can be difficult to distinguish CM from other disorders that present with hypotonia, hyporeflexia, and weakness (eg, DM or congenital muscular dystrophies), the presence of prominent facial weakness with or without ptosis, generalized hypotonic posture with hyporeflexia, poor muscle bulk, proximal muscle weakness, and dysfunction of the respiratory and bulbar muscles are suggestive of CM.[96,97] In most cases, these clinical features contrast with relatively normal development of cognitive abilities and sensation. Severity and onset of muscle weakness and disability vary widely, from neonates with generalized and life-threatening weakness to older patients with subtle proximal muscle weakness.

Cardiac involvement in CM has been reported but is rare.[100] In 143 cases of nemaline myopathy, 6 neonates developed transient HF and 1 infant developed LV dysfunction with congenital long-QT syndrome.[101] In another study with 66 patients with CM, no cardiac lesions were noted[102]; however, hypertrophic,[103–105] dilated,[106–110] and LVNC cardiomyopathy phenotypes,[111,112] as well as sudden death,[113] have been described. Recessive mutations in *TTN* (encoding titin) and *MYH7* (encoding myosin heavy chain-7) have been associated with minicore-like disease, with early development of dilated cardiomyopathy, ventricular arrhythmias, and sudden cardiac death.[114–117]

APPROACH TO CARDIAC EVALUATION IN NMDs

Care guidelines exist for the diagnosis and management of many forms of NMD.[7,118–122] These guidelines are clear that a collaborating team approach results in the best outcomes for patients. Unfortunately, there is often a gap in the translation of clinical care guidelines to practice, and even among knowledgeable neuromuscular and cardiology programs, cardiac involvement can be underevaluated and undertreated. In a recent Cooperative International Neuromuscular Research Group report, >30% of enrolled DMD subjects had not had an echocardiogram, and only 40% of those diagnosed with cardiomyopathy were being treated with cardiac-specific medications.[16] Similar findings were reported by the Pediatric Cardiomyopathy Registry, which also showed that for patients with DMD-associated cardiomyopathy (defined as LVEF <55% or LV shortening fraction <28%), only 30% reported symptoms at cardiomyopathy diagnosis, and survival of patients with DMD with cardiomyopathy was worse than for similarly aged patients with BMD-associated cardiomyopathy or patients with other dilated cardiomyopathies.[13]

The presence of skeletal muscle weakness that results in the use of medical equipment for mobility impacts the symptom complex of many neuromuscular patients, particularly for HF. In the absence of reported symptoms, HF scoring systems, such as the New York Heart Association functional classification,[123] are often falsely reassuring, and the cardiovascular physical examination is often normal. However, marked LV systolic dysfunction can exist without symptoms, and symptoms can be attributed to skeletal muscle weakness rather than HF. There is growing evidence that evaluation and treatment before overt cardiac symptoms appear afford patients the best opportunity for impacting mortality.[21,124] Given that the neurologist most often makes the initial diagnosis of NMDs, a proactive approach should be adopted for referral to cardiology for assessment of cardiovascular condition and management of cardiovascular complications.

Recommendations

1. **NMD providers and patient organizations should promote education regarding the importance of a proactive approach to screening, diagnosis, and management of cardiovascular complications of NMDs and the ideal care team required *(Class I; Level of Evidence B)*.**
2. **All neurologists diagnosing and managing NMDs should work to identify either a cardiologist with expertise in these conditions or at minimum a collaborative electrophysiologist or HF specialist, depending on the condition being evaluated *(Class I; Level of Evidence B)*.**
3. **For conditions diagnosed in childhood, referral to a pediatric HF specialist, when practicable, is reasonable because of evolving diagnostic and management recommendations within pediatric cardiomyopathies *(Class IIa; Level of Evidence B)*.**
4. **Cardiac evaluation should be performed before anesthesia or sedation in any patient with NMD at risk for cardiac involvement. For those with a history or symptoms suggestive of cardiac involvement, cardiac evaluation should be in close proximity (3–6 months) to the anesthesia/sedation event *(Class I; Level of Evidence C)*.**
5. **For NMD patients believed to be at increased cardiac risk during surgery, cardiac monitoring by an anesthesiologist experienced in the care of patients with NMDs should occur during major surgery, and the procedure should take place in a center with appropriate intensive care facilities *(Class I; Level of Evidence C*).**

Cardiac Evaluation in DMD and BMD

Care guidelines for DMD and BMD suggest that cardiac evaluation begin at diagnosis.[4,7,118,119] With the increase in risk of LV dysfunction that occurs with age, ongoing follow-up is also suggested. For DMD, risk of LV dysfunction increases significantly with age, from <5% for boys <10 years of age to >75% for men >20 years of age.[15] For BMD, only a small percentage of patients have clinical symptoms before 16 years of age,[13] increasing to ≈70% with symptomatic HF by age 40 years.[19] Given that therapeutic intervention before symptom onset has a greater impact,[125–129] the detection of abnormal LVEF affords the opportunity to act.[124] Carriers of DMD/BMD

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should undergo cardiac evaluation with any symptoms. At a mean age of 44 years, DMD and BMD carriers have been shown to exhibit both decreased LVEF and evidence of myocardial fibrosis.[130]

In general, there are fewer published references regarding cardiac involvement in BMD than for DMD.[13,19,37,131–137] Approximately 70% of BMD patients develop dilated cardiomyopathy, mostly in the third decade of life or later.[19,132] They rarely develop severe dilated cardiomyopathy in childhood,[138] but when present in childhood, the cardiomyopathy tends to be more severe and progress more rapidly than in DMD.[13,139–142] Cardiac death is more common in BMD than in DMD[19,131,132]; however, this could be because more patients with DMD succumb to respiratory events before cardiac demise. Also, the degree of skeletal muscle involvement in BMD does not correlate with the severity of cardiomyopathy.[132,133]

Cardiovascular imaging plays a key role in screening and management of cardiomyopathy in patients with DMD and BMD. To date, echocardiography has been the primary modality used.[13,19,132,134,143–147] Although electrocardiography is a sensitive method to screen for cardiac disease in BMD,[145,147] it should not replace echocardiography for the detection of preclinical LV dysfunction.[132,148] In addition to standard 2-dimensional, M-mode, and Doppler assessments, research on strain and strain-rate echocardiographic imaging could provide future insights about disease presence and progression before detection of global dysfunction by more traditional echocardiographic indices.[144,149–152] An important limitation in the application of standard transthoracic echocardiography in the care of patients with DMD and BMD is the diminishment of imaging (acoustic) windows because of progression of scoliosis or obesity with advancing age.[153] Thus, the use of other imaging modalities, such as cardiac magnetic resonance imaging (CMR), might better fully characterize the severity of cardiac involvement in older patients.[153]

The role of CMR in the assessment of patients with DMD and BMD is evolving. CMR is capable of providing objective 3-dimensional anatomic analysis, including assessment of ventricular volumes, EFs, and hypokinesia. CMR is also capable of characterizing focal[154,155] and diffuse[156] myocardial fibrosis after intravenous bolus gadolinium contrast injection. In recent studies, late gadolinium enhancement (LGE) was found to increase in prevalence with increasing age (from 17% in DMD patients <10 years old to 59% in those >15 years old) and decreasing LVEF.[157] Typically, LGE in DMD and BMD is subepicardial or midwall progressing to transmural and is located in the inferolateral LV.[148,158–160] Myocardial fibrosis burden, quantified as number of LGE-positive myocardial segments, is associated with decline in EF,[161] and transmural LGE was also recently reported to have additive value above LVEF alone in predicting hospitalization for HF or occurrence of ventricular tachycardia.[162] Abnormalities in segmental circumferential strain, detectable by echocardiography and CMR, may also be an early biomarker of myocardial dysfunction in DMD, preceding the development of myocardial fibrosis.[147,163] There is also emerging evidence that female DMD, and to a lesser extent BMD, carriers have subclinical cardiac involvement, characterized by reduced LVEF or subepicardial LV lateral free wall LGE on CMR.[130]

Although CMR imaging does not suffer from the limitation of poor acoustic windows attributable to body habitus or lung disease, there are factors that may limit its utility for imaging patients with NMDs. CMR might not be feasible for patients who are unable to be comfortably positioned because of immobility or contractures. Also, because CMR image quality is affected by motion, its utility can be limited in patients with tachycardia, arrhythmias, high respiratory rates, or inability to remain still. Although some of these limitations can be overcome with sedation or anesthesia, compromises in respiratory or cardiac function can also impact decision making. Finally, there is potential for artifact leading to CMR image degradation from rods used in the treatment of scoliosis in some NMD patients.

Electrocardiographic abnormalities are commonly observed in DMD. Characteristic electrocardiographic changes include short PR interval, right ventricular hypertrophy, prolonged corrected QT interval, and prominent Q waves in leads I, aVL, V_5, and V_6 or in leads II, III, aVF, V_5, and V_6.[164] Electrocardiography also frequently detects widening of the QRS, with 10 of 48 DMD patients in 1 study having a QRS duration ≥120 ms.[165] Electrocardiography can detect abnormalities at a very early age. In 1 study, 78% percent of steroid-naive DMD patients <6 years of age had electrocardiographic abnormalities, well before the onset of clinical symptoms.[166] Electrocardiographic findings that occur in the late first decade include sinus tachycardia, a tall R wave in V_1, and inferolateral Q waves.[167] In DMD, the presence of QT dispersion on ECG can identify a subset of patients at greatest risk for cardiac death.[168]

Electrocardiographic abnormalities are frequently noted in patients with BMD but are generally nonspecific.[19,132,134,145–147] Rhythm abnormalities are often in proportion to the severity of ventricular dysfunction[21,147]; however, life-threatening ventricular tachycardia has been reported to occur in the absence of significant LV dysfunction.[134]

Periodic ambulatory electrocardiographic monitoring has also been advocated for screening, follow-up, and symptom-directed assessment of arrhythmia in patients with DMD and BMD.[164,169–173] Ambulatory electrocardiographic monitoring can be useful to detect the diminished heart rate variability indicative of sympathetic predominance and increased susceptibility to ventricular arrhythmias.[174,175] However, 2 recent retrospective studies of ambulatory electrocardiographic monitoring

results in 235 DMD patients 14±4 years of age and 91 patients 17±4 years of age found only LVEF <30% to 35% and increased age (eg, ≥17 years) were associated with abnormal ambulatory electrocardiographic findings, such as nonsustained atrial and ventricular tachycardias.[22,23]

Because of limitations in mobility with disease progression, the role of exercise testing in DMD and BMD is somewhat limited.[176–178]

Recommendations

1. **All DMD and BMD patients should have an initial cardiac evaluation with examination, ECG, and imaging performed at diagnosis *(Class I; Level of Evidence B)*.**
2. **Every-2-year cardiac evaluation by examination, ECG, and noninvasive imaging is reasonable in asymptomatic DMD/BMD patients <10 years of age, increasing to annual evaluation at 10 years of age *(Class IIa; Level of Evidence B)*.**
3. **Asymptomatic DMD/BMD patients with LV dilation or dysfunction or arrhythmia (eg, supraventricular tachycardia, ventricular ectopy) should be reevaluated at least annually *(Class I; Level of Evidence C)*.**
4. **Symptomatic DMD/BMD patients should be reevaluated more frequently than annually, with testing and frequency determined by the provider and clinical status *(Class I; Level of Evidence C)*.**
5. **Female DMD/BMD carriers should undergo cardiac evaluation by examination, ECG, and noninvasive imaging in the second to third decade of life, with follow-up evaluations every 3 to 5 years thereafter *(Class I; Level of Evidence C)*.**
6. **Echocardiography should be routinely used in the screening and follow-up care of DMD/BMD patients *(Class I; Level of Evidence B)*.**
7. **It is reasonable to consider periodic use of advanced tissue imaging modalities (eg, CMR with contrast) in the care of DMD/BMD patients for assessment of cardiac function, particularly in patients with poor acoustic windows or for assessment of myocardial fibrosis *(Class IIa; Level of Evidence B)*.**
8. **Ambulatory electrocardiographic monitoring for patients with DMD/BMD is reasonable every 1 to 3 years, based on age, EF, and clinical assessment *(Class IIa; Level of Evidence C)*.**
9. **In the absence of an implantable cardioverter-defibrillator (ICD) or other arrhythmia monitoring, at least annual ambulatory electrocardiographic monitoring is reasonable for patents with DMD/BMD with EF <35% or age ≥17 years *(Class IIa; Level of Evidence B)*.**

Cardiac Evaluation in LGMD

When cardiac disease is present, LGMD1B (LMNA) most commonly manifests arrhythmias and conduction abnormalities, whereas LGMD2C-2F (sarcoglycanopathy) and LGMD2I (FKRP) more commonly show a dilated cardiomyopathy phenotype. Aside from these findings, there are no relevant studies to guide screening and follow-up testing recommendations. Thus, it seems prudent to perform cardiac evaluation near the time of diagnosis, to include physical examination, ECG, and echocardiogram, especially for LGMD2C-2F and -2I patients. Ambulatory electrocardiographic monitoring can be used in LGMD1B patients or with clinical indication.

Recommendations

1. **In patients with LGMD, complete cardiac evaluation should begin at the time of diagnosis and should include examination, ECG, and echocardiography *(Class I; Level of Evidence C)*.**
2. **Follow-up cardiac evaluations to include examination, ECG, and echocardiography every 2 years for asymptomatic LGMD2C-F (sarcoglycanopathy) and LGMD2I patients (FKRP) with normal cardiac findings, and at least annually for those with abnormal cardiac findings, is reasonable *(Class IIa; Level of Evidence C)*.**
3. **LGMD patients with HF or those on HF therapy should be followed up more frequently *(Class I; Level of Evidence C)*.**
4. **Follow-up cardiac evaluations to include examination, ECG, and ambulatory electrocardiographic monitoring should be repeated every 2 years for asymptomatic LGMD1B patients with normal cardiac findings and annually for those with abnormal cardiac findings. Symptoms of palpitations, dizziness, or syncope should prompt additional investigation with ambulatory electrocardiographic monitoring, loop event electrocardiographic recording, or electrophysiology study as warranted *(Class IIa; Level of Evidence C)*.**

Cardiac Evaluation in EDMD

Cardiac disease in EDMD usually presents after the second decade of life, but severe childhood cardio-

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myopathy is possible, and both the timing of onset and severity demonstrate interfamilial and intrafamilial variability.[179–181] Autosomal dominant and X-linked EDMD are associated with bradyarrhythmias, atrial fibrillation (AF)/atrial flutter, heart block, and ventricular dilation with or without systolic dysfunction,[182–184] whereas autosomal recessive EDMD is associated with conduction defects and premature atrial and ventricular contractions.[185] Because sudden death can be the presenting cardiac feature, cardiac screening of individuals with EDMD and first-degree relatives (including female carriers of X-linked EDMD) has been recommended.[186,187]

Follow-up and testing should be dictated by signs or symptoms of arrhythmia or HF, EDMD genotype, and echocardiographic features of dilation or dysfunction. The role of exercise testing remains unclear because of limitations in patients with significant contractures and muscle weakness. For individuals with autosomal dominant EDMD in whom a pacemaker is indicated, consideration of an ICD is warranted.[188] The role of biomarkers, including brain natriuretic peptide, in EDMD is unclear, but brain natriuretic peptide can be used as an adjunctive marker for new diagnosis of cardiomyopathy or to define severity, response to treatment, and progression of cardiomyopathy.[189]

Recommendations

1. **Individuals with EDMD, regardless of genotype, should be referred for cardiology assessment at the time of EDMD diagnosis, even if asymptomatic *(Class I; Level of Evidence C)*.**
2. **At least annual evaluation with echocardiogram, ECG, and ambulatory ECG is reasonable for patients with autosomal dominant and X-linked recessive EDMD *(Class IIa; Level of Evidence C)*.**
3. **Annual ECG and ambulatory ECG are reasonable for autosomal recessive EDMD *(Class IIa; Level of Evidence C)*.**

Cardiac Evaluation in Myofibrillar Myopathies

Because of the inherent genetic heterogeneity among the group of neuromuscular disorders known as MFM, the risk and type of cardiac involvement vary substantially. Cardiomyopathy with MFM can manifest as dilated, hypertrophic, restrictive, or LVNC phenotypes. As with other NMDs, referral to a cardiologist for cardiac assessment should begin with the initial diagnosis. For individuals with poor echocardiographic images, CMR should be considered. Although CMR is more sensitive for detection of early manifestations of LV hypertrophy and LV fibrosis, its use in individuals with normal echocardiograms and MFM to detect early manifestations of cardiac involvement has not been well studied.

Individuals with MFM can develop arrhythmia and electrocardiographic abnormalities. One cross-sectional cohort study of 63 people with MFM reported cardiomyopathy in 16% and arrhythmia or electrocardiographic abnormalities in 25%.[47] Among the various causes of MFM, desmin mutations often cause cardiac conduction disease and life-threatening ventricular arrhythmias.[190] For these individuals, decisions regarding the use of prophylactic ICDs should not depend on EF alone.[191–193]

Recommendations

1. **Cardiology evaluation with examination, ECG, echocardiogram, and ambulatory electrocardiographic monitoring should take place at the time of MFM diagnosis, regardless of symptoms *(Class I; Level of Evidence C)*.**
2. **It is reasonable to reassess asymptomatic patients with MFM annually with examination, ECG, and echocardiography *(Class IIa; Level of Evidence C)*.**
3. **Ambulatory electrocardiographic monitoring or monitoring with a looping event recorder should be performed for assessment of symptomatic palpitations in patients with MFM *(Class I; Level of Evidence C)*.**

Cardiac Evaluation in BTHS

HF is the most common presenting symptom in BTHS. Mortality within BTHS has improved in recent years and likely reflects advances in BTHS recognition and HF management[55]; however, there is a lack of data on which strong, disease-specific recommendations can be based. In clinical practice, follow-up, evaluation, and testing are most commonly dictated by signs/symptoms, age, and cardiomyopathy subtype. Infants with BTHS appear to be at a greater risk of death because of risk of progressive HF, infection, or arrhythmia[55,194]; however, LVNC of BTHS can be associated with a waxing and waning of LV function, and marked improvement or normalization of severe LV dysfunction during the first year of life has been reported.[63] Thus, although heart transplantation might be a therapeutic option, extended medical treatment of severe HF in infancy, in the hope of allowing for recovery at ≈1 year of age, can also be considered.

Echocardiography, electrocardiography, and ambulatory electrocardiographic monitoring are the most commonly used testing modalities, but CMR can be considered in patients with an unclear diagnosis of LVNC or hypertrophic cardiomyopathy or in those with BTHS

with a hypertrophic phenotype to assess for fibrosis and for ICD risk stratification.[195] Exercise testing is of limited utility in BTHS because of significant limitations from both cardiac and skeletal muscle impairments.[196]

Recommendations

1. **Boys should be referred to pediatric cardiology at the time of BTHS diagnosis *(Class I; Level of Evidence B)*.**
2. **At least annual cardiology assessment with examination, ECG, echocardiogram, and ambulatory ECG should be performed in boys with BTHS who have evidence of cardiac dysfunction or HF *(Class I; Level of Evidence B)*.**
3. **Screening of asymptomatic infants with BTHS by examination, ECG, and echocardiogram every 6 months and ambulatory electrocardiographic monitoring every year is reasonable *(Class IIa; Level of Evidence C)*.**
4. **It is reasonable to screen asymptomatic boys with BTHS with examination, ECG, echocardiogram, and ambulatory electrocardiographic monitoring annually *(Class IIa; Level of Evidence C)*.**

Cardiac Evaluation in FA

In FA, consensus guidelines have been published in which cardiac recommendations with respect to assessment and follow-up are based largely on expert consensus.[197] Cardiovascular involvement often manifests initially with electrocardiographic changes, consisting of lateral T-wave inversions, left-axis deviation, and repolarization abnormalities.[198] Ventricular hypertrophy is most commonly observed in patients with FA, with cross-sectional imaging studies showing progressive LV hypertrophy in ≈65% of affected individuals.[72,199] More recent reports suggest that cardiac morphology progresses from normal to concentric biventricular hypertrophy with preserved systolic function and ultimately to a dilated, hypocontractile phenotype because of regression of hypertrophy accompanying myocardial fibrosis.[200,201] The interventricular septal thickness at end diastole has been used to categorize the severity of cardiac involvement in FA; however, the prognostic utility of this scheme has not yet been assessed.[201] Because no relationship between severity of cardiac involvement and neurological status has been identified, regular cardiac evaluation regardless of neurological status is likely warranted.[201]

Echocardiography has been the mainstay of cardiac morphological and functional imaging in FA, but the use of CMR in FA is potentially appealing on the basis of its ability to recognize iron overload.[202] Also, although recent data implicate replacement fibrosis in the pathophysiology of cardiac involvement in FA, the utility of CMR to detect fibrosis and its distribution in FA has not yet been established.[203]

Resting electrocardiographic abnormalities, most commonly T-wave inversion or flattening in the left precordial leads, are more frequent with increasing severity of cardiac hypertrophy.[204] The risk of arrhythmias in FA remains unclear but is believed to increase with increasing severity of cardiac hypertrophy. Tsou et al[74] reported on cause of death among 61 FA patients and found that arrhythmia was the primary or contributing cause of death in 16%. In that study, there were 15 individuals with FA and arrhythmia, with AF being the most common form of arrhythmia (n=11). Guidelines for the management of AF are well established.[205]

Recommendations

1. **Cardiology evaluation with examination, ECG, echocardiogram, and ambulatory electrocardiographic monitoring should occur at the time of FA diagnosis *(Class I; Level of Evidence C)*.**
2. **Asymptomatic FA patients should be followed up at least annually with examination, ECG, and echocardiogram *(Class I; Level of Evidence C)*.**
3. **Symptomatic FA patients should be followed up more frequently than annually *(Class I; Level of Evidence C)*.**
4. **Ambulatory electrocardiographic monitoring or monitoring with an event recorder is reasonable in FA patients with symptoms of palpitations and in those without symptoms every 1 to 4 years, increasing in frequency with increasing age *(Class IIa; Level of Evidence C)*.**

Cardiac Evaluation in DM

Clinical assessment of cardiac involvement in DM should focus primarily on conduction abnormalities, atrial and ventricular arrhythmias, and sudden death.[79,88,89,206,207] Rarely, dilated cardiomyopathy and HF can occur.[208] Thus, patients with DM and their care providers should be questioned as to the presence of syncope, palpitations, or breathlessness,[79,209] and electrocardiographic abnormalities, non–sinus rhythm, prolongation of the QRS interval (particularly with evidence of HV-interval prolongation), PR interval >240 ms, or higher degree of atrioventricular block should be regarded as a risk factor for sudden death.[79,210,211] Because physical exertion has been observed to be a proarrhythmic influence, serial exercise stress testing has been recommended for young DM1 patients.[207] CMR can be requested to noninvasively assess fatty infiltration and fibrosis in the myocardium.[212,213] An electrophysiology study may be indicated in anticipation of pacemaker/ICD implantation

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with syncope or the above-mentioned clinical history or electrocardiographic abnormalities.[37,79,89,206]

Recommendations

1. **Cardiology evaluation with examination, ECG, echocardiogram, and ambulatory electrocardiographic monitoring should occur at the time of DM diagnosis, regardless of symptoms *(Class I; Level of Evidence C)*.**
2. **DM patients with palpitations, dizziness, syncope, non–sinus rhythm, PR interval >240 ms, QRS duration >120 ms, or second- or third-degree atrioventricular block should be evaluated at least annually and also considered for invasive electrophysiology study for possible pacemaker or ICD placement *(Class I; Level of Evidence C)*.**
3. **For DM patients with normal LVEF who lack the features listed in recommendation 2, it is reasonable to reassess by examination, ECG, and ambulatory electrocardiographic monitoring annually and by echocardiogram every 2 to 4 years *(Class IIa; Level of Evidence B)*.**
4. **For young DM1 patients, serial exercise stress testing and signal-averaged ECGs may be considered *(Class IIb; Level of Evidence B)*.**

Cardiac Evaluation in CM

Cardiac disease in CM is rare, and given the diversity of clinical manifestations in the various CMs, there are no evidence-based data to drive guidelines. Many of the genes implicated in various CMs have also been described in patients with cardiomyopathy in the absence of recognized NMD. Thus, it seems prudent to consider the following.

Recommendation

1. **It is reasonable to perform cardiology evaluation with examination, ECG, and echocardiogram at the time of CM diagnosis, with follow-up assessments determined by the presence or development of abnormal findings or cardiac symptoms *(Class IIa; Level of Evidence C)*.**

MEDICATION THERAPY FOR NMDs WITH CARDIAC INVOLVEMENT

Data on the use of HF therapies in NMDs are generally lacking, as highlighted in a recently published collaborative stakeholder working group report on the cardiac care of patients with DMD.[4] Most of the published pharmacological investigations of cardiac care in NMDs are specific to DMD and BMD, and in these nonrandomized, observational studies, it appears that antifibrotic therapies (eg, steroids and angiotensin-converting enzyme inhibitors [ACEIs]) could have a beneficial impact on cardiac function and mortality.[214–216] In the following sections, we attempt to provide a rationale for HF therapies that are commonly used in the care of patients with NMDs, describing disease-specific data on cardiovascular therapies where available.

ACEIs and Angiotensin Receptor Blockers

Inhibition of the renin-angiotensin-system can stabilize or reverse LV remodeling, with multiple studies showing that ACEIs improve symptoms of HF, decrease hospitalizations for HF, improve LV function, and increase survival for adults with symptomatic HF.[217,218] As such, ACEIs are considered a cornerstone of treatment for HF with reduced EF in adults, with benefits in all New York Heart Association functional classifications.

Because of the clear benefits of using ACEIs after the development of dilated cardiomyopathy in adults, as well as the very high prevalence of dilated cardiomyopathy in DMD, a group of investigators in Paris, France, initiated a study of perindopril in boys with DMD and normal cardiac function.[125] They prospectively randomized 57 boys 9.5 to 13 years old to receive perindopril (2–4 mg/day) or placebo. Baseline entry criteria included LVEF >55% by radionuclide imaging, systolic blood pressure ≥80 mm Hg sitting or >70 mm Hg supine, serum blood urea nitrogen ≤20 mg/dL, and ability to tolerate a 1-mg test dose of perindopril. The primary study endpoints were a reduction in LVEF and in the number of patients whose LVEF fell below 45%. After 3 years, LVEF was <45% in a single participant in each arm of the study. The majority of participants continued in an open-label phase in which all received perindopril. At 5 years after randomization, the mean EF was similar in both groups. However, only 1 participant assigned initially to receive ACEIs had an LVEF <45% versus 8 assigned to placebo (P=0.02).[125] The investigators continued the study to assess survival at 10 years, which was a prespecified secondary endpoint. Of the 28 participants initially randomized to ACEI, 93% were alive at 10 years versus 66% of those who were initially assigned to placebo for 3 years.[219] In this study, early versus delayed initiation of treatment with ACEIs conferred a 27% absolute risk reduction in all-cause mortality. All deaths were attributed to a "cardiorespiratory mode," although the investigators acknowledged the difficulty in ascertaining a distinction from a respiratory or cardiac cause.

Although evidence for use of ACEI or angiotensin receptor blocker (ARB) therapy to delay or prevent

onset of dilated cardiomyopathy in NMDs other than DMD is lacking, extrapolation of DMD data to NMDs in which dilated cardiomyopathy is likely to occur is reasonable. Of course, for any patient with NMD and dilated cardiomyopathy, ACEI or ARB treatment is recommended on the basis of clinical trials showing benefits in the absence of NMD.[217,218]

Use of an ACEI carries risks of angioedema, chronic cough, and other side effects that are attributable to the mechanism of action of this category of medications. Selective pharmacological blockade of the angiotensin receptor was developed to bypass this mechanism of action while still achieving favorable neurohormonal antagonism. In studies of symptomatic HF patients who did not tolerate ACEIs, the aggregate data indicate that ARBs are as effective as ACEIs in reducing HF morbidity and mortality.[220] Despite enthusiasm arising from studies showing the potential benefit of ARBs in murine models of skeletal myopathy, use of these medications has not been shown to improve skeletal muscle disease in humans to date.[221]

Recommendations

1. **The use of an ACEI or ARB in the setting of a reduced EF is recommended for all NMDs *(Class I; Level of Evidence B)*.**
2. **The use of an ACEI or ARB before onset of a reduced EF in boys with DMD age ≥10 years may be considered *(Class IIb; Level of Evidence B)*.**

β-Adrenergic Blockade

The recognition of cardiomyopathy leading to HF and arrhythmia risk from childhood through adulthood in various neuromuscular disorders has prompted the proposal that already published guidelines for HF management be similarly used in these disorders.[4] Although there has been clear benefit in the use of β-adrenergic blockade in adult HF with reduced EF, this approach has not uniformly been applied nor routinely studied within the field of neuromuscular cardiology.[222] Despite the largest multi-institutional trial in pediatric HF failing to show the benefit of β-adrenergic blockade similar to adult HF,[223] its use is generally accepted in the setting of HF with reduced EF. This important study began with pilot data from a cohort of diverse HF pathogeneses that included a single DMD subject; however, the main trial excluded NMD-associated cardiomyopathies.[224]

DMD and BMD are the most widely studied pediatric NMDs with cardiomyopathy and HF phenotype. Over the past 2 decades, a number of studies have supported the benefit of β-adrenergic blockade in both symptomatic and even presymptomatic HF with reduced EF in DMD/BMD cardiomyopathy.[124,126,128,225–228] Kajimoto et al[128] evaluated the treatment response of ACEI alone compared with ACEI plus β-adrenergic blockade in a broad range of neuromuscular disorders with reduced EF and showed that the combination of ACEI with β-adrenergic blockade resulted in greater improvement in LV function than ACEI alone. Ogata et al[228] compared the DMD treatment response between asymptomatic HF with reduced EF and symptomatic HF with reduced EF. The application of treatment before symptomatic HF resulted in a 10-year survival rate of 72% compared with 0% for those treated after onset of symptomatic HF. Matsumura et al[124] concluded in their work that β-adrenergic blockade improved survival from death, deterioration in HF, and severe arrhythmia. The average heart rate at enrollment and the reduction of average heart rate correlated with a positive change in EF.[124] Thomas et al[229] initially showed that boys with DMD with normal LV function but with elevated heart rate were more likely to progress to cardiomyopathy than those in the lower quartiles for heart rate. This was followed by the finding that autonomic dysfunction before the onset of HF was associated with myocardial fibrosis, which suggests a role for earlier treatment.[173] These studies suggest similar benefits to those seen in adult HF, with improvement in LVEF and mortality, and possibly greater benefit than has been seen in pediatric populations of diverse HF pathogeneses.

The use of β-adrenergic blockade in patients with reversible airway disease has traditionally been cautioned against for fear of adverse respiratory events.[230] More recent studies suggest that adverse respiratory events are not associated with cardioselective β-adrenergic blockers (eg, metoprolol) in adults.[231,232] Current pediatric HF management guidelines call for slow uptitration when β-adrenergic blockers are used.[189]

Unfortunately, there continue to be mixed results when animal models and human studies are compared. Blain et al[233] treated 8-week-old mdx (a model of DMD) and Sgcd$^{-/-}$ (a model of LGMD) mice with β-adrenergic blockade. Although improvement in measures of LV function was observed in the mdx model, there was no effect on increased in vivo calcium influx and deleterious effects on RV function. In addition, no effect was seen in the Sgcd$^{-/-}$ model. This group had previously shown β-adrenergic blockade therapy resulted in improved afterload and contractility for mdx, but the same treatment applied to Sgcd$^{-/-}$ resulted in cardiovascular deterioration and even increased mortality to dobutamine challenge.[234] Most recently, data on combination β-adrenergic blockade and ACEI therapy in mdx mice showed no additive benefit to treatment with either alone.[235]

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Recommendations

1. **Given the balance of human data regarding the use of β-adrenergic blockade in DMD/BMD and, to a lesser extent, other neuromuscular disorders, the use of β-adrenergic blockade in the setting of any NMD with a reduced EF is recommended *(Class I; Level of Evidence B)*.**
2. **Without other indication (eg, arrhythmia), the use of β-adrenergic blockade in the absence of reduced EF as therapy to delay or prevent onset of dilated cardiomyopathy is currently not recommended *(Class III; Level of Evidence C)*.**

Mineralocorticoid Antagonists

The benefits of aldosterone blockade in adults with HF are well described and might be attributable to a combination of decreased collagen deposition, decreased hypertension, decreased vascular inflammation, improved endothelial function, and stabilizing repolarization.[236–247] Aldosterone blockade by spironolactone was shown to reduce all-cause mortality in adults with symptomatic HF by 35% when it was added to standard HF therapy in the RALES trial (Randomized Aldactone Evaluation Study).[248] Subsequently, eplerenone was found to provide a similar survival benefit in adults with HF caused by LV dysfunction[249,250] In addition to improving survival and hospitalization rates, canrenone and spironolactone have been associated with reverse remodeling in adults with HF.[251,252] There is extensive experience with the use of spironolactone in children as a potassium-sparing diuretic, and some pediatric HF specialists routinely use low-dose aldosterone blockade in children with symptomatic HF, extrapolating potential benefit from adult data.

There are emerging data to suggest that aldosterone blockade could be beneficial in patients with DMD. A study in mdx mice found that treatment with a combination of lisinopril and spironolactone preserved both skeletal muscle and myocardial function compared with untreated mice.[253] A subsequent randomized, placebo-controlled trial of boys and young men with DMD treated with background ACEI or ARB found that the addition of eplerenone resulted in better preservation of LV circumferential strain measured by CMR.[254] Although it is well known that hyperkalemia is a side effect of aldosterone blockade, and potassium levels must be monitored in patients taking aldosterone antagonists, no hyperkalemia was noted in this trial.[248,249,254] A noninferiority trial is ongoing to compare spironolactone and eplerenone in boys and young men with DMD. Although these early results are promising, the relatively short duration of follow-up and the lack of confirmatory studies make their long-term benefit unknown. Furthermore, the age at which initiation of aldosterone blockade can provide benefit in the absence of ventricular dysfunction is unknown.

Recommendations

1. **Given the evidence of benefit in adults with symptomatic LV systolic dysfunction, it is reasonable to consider the use of an aldosterone antagonist in DMD/BMD with systolic dysfunction *(Class IIa; Level of Evidence C)*.**
2. **Use of an aldosterone antagonist in DMD/BMD and with preserved LV systolic function, particularly in those who have evidence of myocardial fibrosis (eg, LGE on CMR), may be considered *(Class IIb; Level of Evidence C)*.**

Glucocorticoids

The use of glucocorticoids to lengthen the delay to loss of ambulation in DMD patients is well supported by clinical trial and natural history study data[9,255] and is the recommended standard-of-care treatment of DMD.[7,256] To date, a number of uncontrolled retrospective patient analyses have suggested that glucocorticoid treatment could delay or be protective against the development of DMD-related cardiomyopathy.[17,214,215,257,258] The most recently published study reported an all-cause mortality benefit, primarily on the basis of cardiac mortality, for glucocorticoids in a propensity matched analysis of 86 patients with DMD[215]; however, this study included patients born as early as 1972 and did not control for era, which raises the concern that life-extending advances in DMD care, including respiratory advances, could have confounded the results. Furthermore, others have found no beneficial association of glucocorticoids on cardiac outcomes.[16,146,259] Currently, there are no data to support the use of glucocorticoids to improve or stabilize cardiac function in other NMDs.

Recommendations

1. **The use of glucocorticoids to slow the progression of cardiac disease in patients with DMD may be considered *(Class IIb; Level of Evidence B)*.**
2. **The use of glucocorticoids in patients with other NMDs (including BMD) should be guided by noncardiac indications for treatment *(Class I; Level of Evidence C)*.**

Diuretic Agents

Studies of diuretic therapy in adults have demonstrated improvement in physical signs of fluid overload, symp-

toms of HF, exercise tolerance, and stroke volume[260–263]; however, no survival benefit has been shown, and the use of diuretic agents should be tempered by the potential for harm by intravascular volume depletion, electrolyte abnormalities that predispose to life-threatening arrhythmias, and increased levels of renin, angiotensin II, and aldosterone.[43,264–267] Because the use of diuretic agents for children with HF associated with NMD is similar to use for other pediatric HF indications, our recommendations are in line with recent pediatric HF guidelines.[189]

Recommendation

1. **Patients with NMD and fluid retention associated with ventricular dysfunction should be treated with diuretic agents to achieve a euvolemic state *(Class I; Level of Evidence C)*.**

Anticoagulation

Neither clinical experience nor the literature suggests that children with NMDs have a higher incidence or risk of venous or systemic thromboembolism; however, certain NMDs are associated with systolic ventricular dysfunction or arrhythmias, such as atrial flutter or fibrillation, which could be indications for the use of anticoagulation or antiplatelet agents.[189,268,269] Also, patients with BTHS may be at increased risk of systemic arterial thromboembolism related to ventricular noncompaction phenotype.[270,271]

Adults with low EF are known to be at increased risk of intracardiac thrombus formation with thromboembolism. The risk of thrombus ranges from 1.4% to 4.2% per 100 patient-years or 1% to 3% per year (depending on the study), and echocardiographic evidence of intracardiac thrombus has not correlated with the rate of embolism.[272–276] The hypercoagulable state found in HF is attributable to a combination of stasis, platelet activation, increased blood viscosity, and increased fibrinolytic activity.[277–279] Studies of adults in sinus rhythm with HF and systolic LV dysfunction have not shown a clear difference in the incidence of stroke when warfarin and aspirin were compared to warfarin alone.[280–283] There are no similar prospective data available in children with systolic ventricular dysfunction, and the true risk of thromboembolism is unknown, regardless of NMD status.[284–291]

It is well established that thrombosis prevention is indicated in adults with AF/atrial flutter in the absence of ventricular dysfunction, and extremely detailed risk-based guidelines for anticoagulation in AF/atrial flutter exist[205]; however, data in children and those with NMDs are lacking. A study of arrhythmias in NMD described AF/atrial flutter in 139 patients with laminopathy (lamin A/C), MFM, DM1 and DM2, DMD, BMD, EDMD, LGMD, or facioscapulohumeral muscular dystrophy.[292] Stroke or embolism was observed in 6.5% of the patients, none of whom were undergoing oral anticoagulation therapy before stroke, and the authors suggested that oral anticoagulation is only indicated for NMD patients who also meet an additional risk factor (eg, HF, prior stoke or transient ischemic attack, hypertension).[292] This would appear to be at odds with recommendations for anticoagulation in patients with AF/atrial flutter.

Recommendations

1. **Aspirin or low-dose anticoagulation therapy may be considered for patients with BTHS and noncompaction phenotype *(Class IIb; Level of Evidence C)*.**
2. **Thrombosis prophylaxis in children with NMDs, normal systolic ventricular function, and AF/atrial flutter may be considered, with type of therapy determined based on the individual patient's thrombosis risk *(Class IIb; Level of Evidence C)*.**
3. **Anticoagulation or antiplatelet therapy is not recommended for patients without a history of arrhythmia who have NMDs in which cardiac involvement commonly manifests as arrhythmia *(Class III; Level of Evidence C)*.**

Antiarrhythmic Drugs in NMDs

Aside from the caveat that class I, II, or IV antiarrhythmic agents can increase peripheral muscular weakness,[293] the use of antiarrhythmic drugs in patients with NMDs is the same as for patients without NMDs. Treatment decisions should be tailored to the unique clinical circumstances of each patient, with consideration of any coexisting conduction abnormalities or myocardial dysfunction.[294,295]

OTHER THERAPIES AND CONSIDERATIONS FOR NMD-ASSOCIATED CARDIAC DISEASE

Exercise, Physical Therapy, and Weight

In addition to the variety of cardiac involvement outlined above, poor cardiorespiratory endurance is common in patients with NMD, and the capacity to respond to aerobic training is not clear. For some NMDs, there exists a cycle in which gradual loss of strength leads to a sedentary lifestyle, which leads to deconditioning and further intolerance or disincentive for activity.[296] At least 2 small studies have suggested that patients with progressive NMDs are at increased risk of adiposity because of reduced physical activity

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and multiple cardiovascular and metabolic risk factors.[297,298] Although physical activity is well recognized to maintain cardiovascular and metabolic health in the general population,[299] as well as in certain populations with heart disease, including HF patients,[300] the impact of exercise in patients with NMDs is unknown. Furthermore, the role of strengthening exercises is controversial in progressive NMD because of concern about precipitating muscle breakdown. Current consensus is that submaximal effort strengthening regimens, designed to avoid disuse atrophy while preventing exercise-induced muscle injury and disease progression, are probably safe and appropriate.[301,302] Wright et al[296] examined the effects of a 12-week walking program in adults with slowly progressive NMD and found that walking 15 to 30 minutes 3 to 4 days a week at 50% to 60% of heart rate reserve produced very modest but statistically significant decreases in submaximal heart rate and systolic blood pressure. Whether such exercise is capable of producing meaningful benefits to significantly impact the trajectory of cardiac involvement in patients with NMDs is not known.

Assisted Ventilation

Advances in management of respiratory muscle weakness and ventilation have undoubtedly improved survival for patients with DMD and likely for those with other NMDs.[14,18] Whether these advances positively impact NMD-associated HF or arrhythmia is unknown. NMDs can result in restrictive lung disease, with elevation in pulmonary artery pressure attributable to thoracic cage deformities or respiratory muscle weakness.[303] Several studies have shown a correlation between the severity of sleep-disordered breathing and cor pulmonale in NMD patients who demonstrate alveolar hypoventilation during sleep.[304,305] Although no prospective studies have addressed the issue, resolution of hypoxemia and noninvasive positive-pressure ventilation appear to improve cor pulmonale in patients with restrictive lung disease.[306] Furthermore, the possible benefit on HF of alleviating central sleep apnea is an area of active investigation. Central sleep apnea with Cheyne-Stokes respiration is common in adults with HF and is associated with ventricular arrhythmias and sympathetic nervous system activation.[307–309] Supplemental analysis of a randomized, controlled clinical trial of 258 HF patients with central sleep apnea and no NMD showed that effective continuous positive-pressure ventilation is associated with increases in LVEF and improved heart-transplant free survival[310]; however, a more recent prospective randomized trial testing the efficacy of adaptive servo-ventilation for central sleep apnea in HF with reduced EF showed that this therapy was associated with increased mortality.[311] Further investigation of the cardiac impacts of continuous positive-pressure ventilation in this population is warranted.

Finally, the role of spinal surgery for the correction of scoliosis in patients with NMD and associated thoracic rib cage/restrictive lung disease is an area of uncertainty, and the application of these technologies for the benefit of cardiac involvement is premature. A recent Cochrane database review concluded that no evidence-based recommendation can be made for spinal surgery in DMD because of the lack of randomized, controlled clinical trials.[312] Although studies have reported potential advantages of spinal surgery, including increased comfort and sitting tolerance, cosmetic improvement, and pain relief,[313–316] there is no clearly demonstrated effect of spinal fusion on the natural deterioration of respiratory function in DMD.[316–321] There is also debate about improvements in life expectancy, with both lower mortality and no difference in mortality after spinal surgery for DMD having been reported.[317,318,321,322]

Cardioverter-Defibrillator and Resynchronization Therapy

In patients with nonischemic cardiomyopathy, standard criteria for primary ICD therapy include class II or III HF with LVEF of ≤35% despite medical therapy.[21] At present, there are no national guidelines that support ICD implantation using other criteria.[21] Because the incidence of ventricular arrhythmias and sudden death is relatively high in certain forms of NMD (DMD, BMD, EDMD, DM1, FA, LGMD1B), some have proposed a broader application of ICD therapy.[323] In some NMDs, risk factors for sudden death have been elucidated. For example, in LGMD1B and EDMD, risk factors include nonsustained ventricular tachycardia, EF <45%, male sex, and lamin A/C mutation.[324,325] For individuals with the *LMNA* mutation who require a pacemaker, placement of an ICD instead, regardless of EF, is indicated.[188,191] Female carriers of X-linked EDMD are also at risk of sudden death, usually later in life,[21] as are some patients with advanced DMD and BMD. Thus, these high-risk patients can be considered for ICD therapy despite the absence of the usual criteria. However, the risks of psychological harm and procedural or device-related complications (eg, inappropriate discharge) and the consensus guideline recommendations against ICD placement in the context of terminal illness or limited life expectancy[326] mandate a thoughtful and individualized discussion before placement of an ICD in any patient with NMD.[327] There can also be confounding issues presented by the extent of the neuromuscular disorder. The presence of severe kyphoscoliosis and respiratory muscle weakness could increase the risks associated with ICD placement in the patient with advanced DMD.[4]

Because conduction system disease and the need for right ventricular pacing frequently accompany severe LV dysfunction in advanced NMD, biventricular pacing or

resynchronization therapy may be an option, particularly in DMD or BMD.[20,328] To date, there are only a few case reports of benefit with cardiac resynchronization therapy in DMD,[329,330] BMD,[331] and DM1.[332,333]

Recommendation

1. **It is reasonable to consider ICD placement in select NMD patients, particularly in NMDs in which arrhythmia may be a predominant feature (DMD, BMD, EDMD, DM1, FA, LGMD1B), after thoughtful discussion and decision making, which should be individualized and based on the overall medical status and options for management *(Class IIa; Level of Evidence C)*.**

End-Stage HF

The role of mechanical circulatory support (MCS) for patients with NMDs has not yet been well defined. At present, there are only a handful of reports on the use of ventricular assist devices in patients with NMDs.[334–339] These reports acknowledge that perioperative risk is likely to be higher than in the general population because of concomitant skeletal muscle weakness or restrictive lung disease.[334–339] Before durable MCS placement, careful consideration must also be given to how atypical thoracic anatomy attributable to kyphoscoliosis in some NMDs might impact device selection and positioning, as well as the potential need for invasive pulmonary support with tracheostomy and reliable delivery of nutrition via permanent gastrostomy tube after durable MCS placement. Finally, the significant burden that outpatient MCS places on caregivers should be contemplated before placement.

Individuals with advanced NMD have typically not been considered candidates for cardiac transplantation out of concern that the multiple morbidities of advanced NMD (eg, respiratory insufficiency, dysphagia, sedentariness) unacceptably limit the benefits or increase the risks of transplantation.[340] However, cases of successful heart transplantation have been reported for patients with BMD, LGMD, EDMD, BTHS, and DM, in which cardiomyopathy can be disproportionally severe relative to skeletal and respiratory muscle impairment.[60,337,341–347]

The use of home inotropic support can be considered in patients with end-stage HF who are not candidates for MCS or heart transplantation. The use of home inotropic therapy might be an option for some patients with end-stage HF who are not candidates for other therapies, because this approach can alleviate symptoms and allow for hospital discharge.[222,348–350] Adult patients with NMD with end-stage HF should be managed on the basis of existing guideline recommendations with appropriate treatment of comorbidities.

Recommendations

1. **Durable MCS may be considered in carefully selected patients with NMD and end-stage HF as a bridge to cardiac transplantation or as destination therapy (*Class IIb; Level of Evidence: C*).**
2. **Cardiac transplantation may be considered in carefully selected patients with NMD and end-stage HF despite appropriate therapies *(Class IIb; Level of Evidence C)*.**
3. **The use of home parenteral inotropic therapy may be considered for treatment of carefully selected patients with NMD as palliative therapy for symptom control in the setting of stage D HF despite optimal management *(Class IIb; Level of Evidence C)*.**

Transition of Care

Transition of patients with special healthcare needs from pediatric to adult care providers is now recognized as an essential step in the management of adolescents and young adults.[351,352] Approximately 750 000 children with special healthcare needs in the United States transition to adult care annually, and <50% receive adequate support and the services needed to realize an effective transition.[353–355] Early development of staged and timely transition processes and programs geared toward education, and modifiable for individualized patient diagnosis and complicit concerns, is greatly needed.[356–360] It is recommended that education through accurate dissemination of information begin at an early stage in the patient healthcare process and directly involve caregivers, providers, support staff, and the patient.[351,361–363] Patients with NMDs are likely to benefit from a coordinator-directed, multidisciplinary team approach, which can provide important support in negotiating communication gaps between providers and enable a systematic clinical transition and education process on health, adult care providers, facilities, and financial and medical resources.[351,353,358,364,365]

Supportive Care

Patients with severe forms of NMD are now living well into adulthood, resulting in previously unstudied management considerations. Populations with NMDs may have significant symptom burden, including chronic pain, fatigue, dyspnea, and edema. Treatment strategies to address cardiac symptoms in NMD patients may include complex decision making for the patient, family, and healthcare providers. In this context, palliative care specialists can be an invaluable resource in facilitating complex decision making and ensuring access to appropriate resources for the planned path of care.[366]

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The integration of palliative care can occur at any point during the course of a chronic illness such as NMD and can be used throughout the entire course of care.[367] Palliative and supportive care are recommended in the effective care of advanced symptomatic HF and NMD, because such interventions are associated with improved quality of life in heterogeneous HF populations.[222] The integration of palliative care into comprehensive NMD management can alleviate suffering and may prolong life.[368] Palliative care should be considered for those patients with NMD who are admitted with HF, especially those with multiple admissions for HF, given the progressive nature of both diseases and significant morbidity and mortality secondary to symptomatic HF.[369,370] Palliative care should be included in the evaluation of all patients being considered for MCS or cardiac transplantation.[222,371]

Palliative care should also be involved in advance care planning and the development of advance care directives. A combination of the HF and palliative care teams is typically best positioned to assist families in making decisions regarding end-of-life care. For those patients receiving destination therapy MCS, patient and family preferences for end-of-life issues should be included in the palliative care discussion.[371] End-of-life issues should be discussed with a patient-centered approach and should include treatment goal clarification and advance care planning or development of advance directives. In those patients receiving MCS, there should also be discussion about future device disablement.[372,373] These discussions should be revisited periodically, because patient and family views can change through the course of the disease. In the United States, patients with end-stage HF may be considered for hospice services.[374] Hospice care is frequently underused, but a referral to hospice may be appropriate for patients with a short life expectancy.

Recommendations

1. **Palliative and supportive care is recommended for patients with NMD and significant heart disease, including those receiving advanced HF treatments such as MCS or transplantation, and should be instituted early in the course of management *(Class I; Level of Evidence C)*.**
2. **The multidisciplinary team, including palliative and supportive care, should discuss end-of-life issues, including advance directives and a living will, before MCS implantation in adults (and appropriate adolescent patients) with NMD and end-stage HF *(Class I; Level of Evidence C)*.**
3. **It is reasonable to consider hospice care for all NMD patients with significant HF with a life expectancy of <6 months *(Class IIa; Level of Evidence C)*.**

SUMMARY AND FUTURE DIRECTIONS

The continued improvement in survival and quality of life for individuals with NMD over the past several decades has been astounding; however, cardiac impairment represents a major obstacle to further improvements. As such, it is critical that the cardiac community devote resources to enhancing cardiac outcomes in this population. These advances can occur through mechanistic studies, pooling of data through registries, adherence to proven therapeutic interventions, and prospective trials. There are several key topics that require particular attention. These focus areas include the role of glucocorticoids in myocardial protection in DMD, the optimal timing for use of standard HF medications to prevent or delay the onset of myocardial impairment in NMD, the clinical impact of myocardial fibrosis in various NMD states, and the utility and ethics of advanced therapies such as implantable defibrillators, MCS, and cardiac transplantation in advanced HF secondary to NMD. Furthermore, advances in understanding of disease- and mutation-specific pathogenesis are vitally important to the goal of care recommendations that are tailored precisely to each specific NMD and are proven to be beneficial.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Modest.

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