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Current Concept Review

Orthopaedic Management in Duchenne Muscular Dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy and occurs primarily in males, affecting 1 in 3600–6000 live male births. The natural course of DMD results in a profound, progressive decline in muscle strength, requiring the use of a wheelchair, typically by age 13, and ultimately leading to fatal respiratory and cardiac dysfunction by young adulthood. Musculoskeletal care for patients with DMD often centers around preventing and managing contractures, fractures, and scoliosis. Medical considerations that affect musculoskeletal care include osteopenia and osteoporosis, endocrinopathies, and pulmonary diseases, which often affect perioperative care. This study aims to provide a detailed and updated review of current treatment options for DMD, highlighting the role of novel treatment options (eg gene therapy) that are changing the landscape of care for the DMD population.

Key Concepts:

(1) Orthopaedic management of patients with Duchenne muscular dystrophy centers primarily around mobility preservation and managing contractures, scoliosis, and fractures.
(2) Perioperative considerations include cardiology (ie preoperative echocardiogram for assessing cardiomyopathy progression), pulmonology (ie sleep-related breathing disorders that may result in compromised respiratory function intraoperatively), endocrinology (ie chronic glucocorticoid use that should not be paused in the perioperative period to prevent adrenal crisis), and anesthesiology (ie avoidance of depolarizing muscle relaxants).
(3) As new gene-modifying treatments become available, the orthopaedic management of patients with Duchenne muscular dystrophy will continue to evolve rapidly.

Introduction

Duchenne muscular dystrophy (DMD) is an inherited neuromuscular disease that results in muscle wasting and premature death. DMD is the most common childhood muscular dystrophy and occurs primarily in males, affecting 1 in 3600–6000 live male births [1]. Early signs of DMD include plateau and regression of early motor milestones and proximal muscle weakness, presenting as difficulty with running and jumping [1]. On average, children are initially diagnosed at age five due to marked divergence in motor function compared with their peers [2].

As sequelae of progressive muscle weakness, patients with DMD are prone to joint contractures and osteoporosis, the combination of which results in a higher risk of fracture [3]. Scoliosis is also a common orthopaedic issue in adolescence. A multidisciplinary approach to caring for patients with DMD, including, but not limited to, orthopaedic surgeons, pediatricians, cardiologists, pulmonologists, neurologists, and physical therapists, is critical to prolonging ambulation and improving quality of life [3].

Treatment guidelines are helpful for orthopaedic surgeons and other treating practitioners to develop personalized plans for their patients. However, none of the available guidelines contain detailed information about novel therapies, such as gene therapy [3,4]. We aim to provide a thorough and updated review of current treatment options for DMD, highlighting the role of novel treatment options that are changing the landscape of care for patients with DMD.

Pathogenesis

DMD is an X-linked dominant condition resulting from dystrophin gene mutations [1]. Dystrophin is a protein primarily expressed in the skeletal and cardiac muscles, with smaller amounts in the brain [5]. The primary role of dystrophin is to anchor the sarcolemma to the underlying

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cytoskeleton and to protect the sarcolemma from stress during muscle movement [6]. Mutations result in the absence or improper function of the dystrophin protein, leading to progressive muscle degeneration and dysfunction.

The natural course of DMD results in a profound, progressive decline in muscle strength, requiring the use of a wheelchair typically by age 13 [7] and ultimately leading to fatal respiratory and cardiac dysfunction by young adulthood [1]. Recent systematic reviews report an average life expectancy of 28–32 years [8,9]. Milder allelic forms of the disease, including intermediate muscular dystrophy (IMD) and Becker muscular dystrophy (BMD), may result in delayed progression, with loss of ambulation at 13–16 years and greater than 16 years old, respectively [1]. Although distinctions between the different forms of muscular dystrophy may be subtle and along a spectrum, proper identification is essential to providing accurate prognoses to clinicians and families (Table 1).

Disease progression in female carriers of DMD is more variable when compared with affected males. 10% of female carriers of DMD have clear disease manifestations [1], such as a milder form of skeletal muscle disease [4]. Female carriers are also at an increased risk of experiencing cardiomyopathy, with one study finding that 47% of carriers had at least one positive finding on cardiovascular magnetic resonance imaging (ranging from subtle cardiac abnormalities to cardiomyopathy) [15]. While no carrier-specific treatment guidelines exist, accepted treatment practices align with other genetic cardiomyopathies, including screening for cardiac abnormalities every 3–5 years [4].

Diagnosis and screening

Even without a family history, DMD should be suspected in a child with abnormal muscle function (eg absent deep tendon reflexes, pain in calves with activity), increased serum creatine kinase, and elevated transaminases [1]. Early symptoms include plateau and delays in meeting developmental milestones or loss of earlier obtained motor milestones, such as independent walking and language, calf pseudohypertrophy (Fig. 1), a waddling gait (video 1), and a positive Gower sign (video 2) [1]. In children younger than five years old, a normal motor function examination is insufficient to exclude a DMD diagnosis. In contrast, the diagnosis can be excluded in older children with a normal muscle examination [1].

Increased sarcolemma permeability in children with dysfunctional dystrophin leads to creatine kinase release from muscle fibers [16]. As such, creatine kinase levels can be used to screen for DMD and other muscular dystrophies [17]. Screening should be performed for all children with a family history of DMD [1]. Regardless of family history, however, there should be a low threshold for obtaining serum creatine kinase in any child suspected of having DMD or other muscle disorders. Newer technology has allowed for more widespread screening for DMD. In December 2019, the Food and Drug Administration authorized a DMD screening kit that measures creatine kinase-MM levels in dried blood specimens. This screening technology allows for the identification of carriers and patients with DMD and BMD [17]. Newborn screening for DMD has become standard in New York (https://www.nysenate.gov/legislation/bills/2023/A5042), Ohio (https://codes.ohio.gov/ohio-revised-code/section-3701.501), and Minnesota (https://www.health.state.mn.us/news/pressrel/2024/newborn012624.html).

Table 1.
Notable allelic forms of Duchenne muscular dystrophy.

Patient Population	Phenotype presentation
Male and female patients	Isolated cardiac phenotype [10–12]
Female patients	Phenotype presenting in 10% of female carriers who may have cognitive and/or cardiac symptoms [13,14]
	Phenotype in female carriers who may have disease severity similar to that which is seen in affected males [13,14]

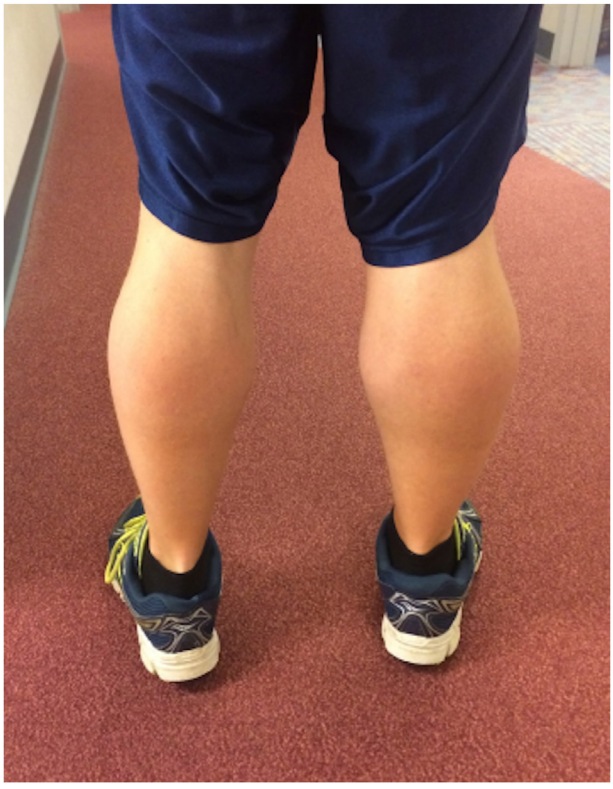

Figure 1. Calf pseudohypertrophy in a male with Duchenne muscular dystrophy.

After a positive screening, DMD was historically diagnosed via muscle biopsy [1]. With advances in gene sequencing, the current standard diagnostic method utilizes multiplex ligation-dependent probe amplification (MLPA) of blood or saliva to test for common copy number aberrations [18,19]. Muscle biopsy may be an alternative diagnostic method should clinical suspicion remain high despite negative or inconclusive genetic testing.

Important medical considerations

Management of DMD necessitates a multidisciplinary approach, focusing on preventative measures and active interventions [20]. Implementing multidisciplinary care coordination can improve patients' function, quality of life, and longevity and facilitate clinical trials by laying out an infrastructure for identifying patients, initiating appropriate interventions, and collecting necessary data (eg functional assessments, blood samples, etc.) [20]. Clinics should ideally include providers from the following specialties: rehabilitation, orthopaedics, pulmonology/respiratory therapy, cardiovascular, gastroenterology/nutrition, pain management, endocrinology, general surgery, neurology, and emergency medicine [20,21].

For procedures that may require the administration of general anesthesia, an echocardiogram and electrocardiogram may be necessary for preoperative assessment, given the high prevalence of cardiomyopathy in the muscular dystrophy population. The sole use of intravenous anesthetic is recommended because inhalational anesthetic agents (eg halothane and isoflurane) may result in rhabdomyolysis and other cardiac complications [20,22]. Depolarizing muscle relaxants, such as succinylcholine, are contraindicated as their use may be fatal. Blood loss should be minimized with mildly hypotensive anesthetics, crystalloid fluid, and cell-saver technology for spinal fusions [20]. Glucocorticoids that are currently being used should be continued throughout to prevent adrenal

crisis. Noninvasive assisted ventilation and chest physiotherapy (cough-assist) should be used after surgery for patients with significant respiratory muscle weakness, which can be identified with preoperative pulmonary functional testing (Table 2) [20].

Systemic diseases for the orthopaedic surgeon to consider

Osteopenia and osteoporosis

Patients with DMD are prone to fracture as a sequelae of disuse osteopenia and chronic glucocorticoid therapy [4]. Of patients with DMD, 20%–60% will experience lower extremity trauma fractures in their lifetime, while 30% will develop symptomatic vertebral fractures [4]. The current standard of care is to identify and treat early indications of bone fragility (eg vertebral fracture), as existing guidelines have not identified a gold-standard medication for preventing first-ever fractures [4,23,24]. Patients with DMD should undergo dual-energy X-ray absorptiometry (DEXA) scans before initiation of glucocorticoid therapy and every one to two years after that [25,26]. Following a low-energy vertebral or long-bone fracture, bisphosphonate therapy can be considered. Given the risk of esophagitis with oral bisphosphonates, IV bisphosphonate therapy may be better tolerated [27]. The effect of prophylactic bisphosphonate use on fracture prevention in patients with DMD appears to be well-tolerated and may even provide a survival benefit [28,29].

Endocrinopathies

Short stature is common in patients with DMD, with glucocorticoid therapy being the primary cause [30]. Linear growth should be evaluated every six months until the completion of puberty [21]. Additionally, low levels of testosterone, often associated with chronic glucocorticoid use [30], can cause hypogonadism and delays in puberty in boys with DMD [21]. While testosterone replacement therapy may help treat hypogonadism; it also may result in premature physeal closure [21]. Conversely, testosterone may be beneficial in this patient population to induce earlier puberty, thereby increasing muscle mass, accelerating growth, and leading to sexual maturation [30,31]. Yet, there is a lack of literature examining whether the use of testosterone increases ambulant time or affects fracture risk. As such, the benefits of testosterone replacement for hypogonadism should be weighed against the risk of further growth impairment.

Pulmonary diseases

Respiratory function should be monitored, and complications such as mucus plugging, atelectasis, and respiratory failure should be anticipated [4]. Patients often require respiratory support in the early nonambulatory stage, with possible interventions including assistive cough devices, noninvasive ventilators, and tracheostomy [4]. Given that children with DMD are at an increased risk of developing sleep-related breathing disorders [32], sleep studies should be performed annually, starting when patients begin to use wheelchairs, to ensure that they do not become apneic at night [4,33]. Early identification of pulmonary decline and sleep-related breathing disorders can help surgeons and anesthesiologists determine appropriate perioperative management (Table 2).

Disease progression

Unfortunately, longitudinal natural history studies that describe DMD are lacking [21]. Yet glucocorticoids, along with novel gene therapies, have increased the lifespan of children with DMD [34]. As such, guidelines for the orthopaedic management of patients with DMD must reflect these new trajectories of disease progression. While there are no strict definitions of the stages of DMD, for this review, aligned with previous literature, we divide the discussion of the course of DMD into the following stages: diagnosis, early ambulatory, late ambulatory, early nonambulatory, and late nonambulatory [20].

Orthopaedic management of DMD

Ambulatory stage

For patients in the ambulatory stage, contracture management is critical to preserve mobility. Stretching and orthoses are first-line therapies for contracture prevention [3]. Surgical intervention is considered only for patients with severe contractures who are otherwise strong ambulators [3]. Ankle plantar flexion contractures are often the first to develop in patients with DMD, followed by knee flexion, hip flexion, elbow flexion, wrist flexion, and forearm supination contractures [35,36]. While stretching, splinting, standing devices, serial casting, and surgical interventions may be useful in treating contractures; there is limited evidence for or against their efficacy [37].

Broadly, surgical intervention is not recommended in the early ambulatory stage but may be beneficial for the middle ambulatory stage to improve late-stage ambulation [3]. Generally, surgery should not be performed on the hips or knees [3]. However, surgery on the foot and the Achilles tendon may improve gait in patients with ankle contracture who still have sufficient quadriceps and hip extensor strength [3]. For an equinovarus foot deformity, a lengthening or tenotomy of the flexor hallucis longus, flexor digitorum longus, and posterior tibial tendon may be considered along with Achilles tendon lengthening [3]. Posterior tibial tendon transfer may benefit patients with varus foot positioning and can assist in active dorsiflexion [3]. Postoperatively, patients should walk in short leg casts on the first or second postoperative day and may benefit from ankle-foot orthoses for ambulation after casts are removed [3].

Throughout all stages, patients should undergo spine monitoring. The onset of scoliosis in an ambulatory patient is unusual, but curves should be assessed annually [3]. Visual assessment (eg through Adams' forward bend test) should be sufficient during the ambulatory stage [3]. If a curve

Table 2.
Surgical considerations for patients with Duchenne muscular dystrophy.

Time Point	Provider	Considerations
Preoperative	Cardiology	Echocardiogram and electrocardiogram should be performed before the use of general anesthesia
	Pulmonology	Assess baseline respiratory status with pulmonary function testing
	Endocrinology	Preoperative glucocorticoid regimen should be continued throughout the perioperative period to avoid adrenal crisis
Intraoperative	Anesthesiology	Intravenous anesthetic technique should be used
		Avoid inhalational agents and depolarizing muscle relaxants
		Minimize blood loss using mildly hypotensive anesthetics, crystalloid fluid, and cell saver technology
Postoperative	Pulmonology	For patients at high risk of postoperative pulmonary decompensation (FVC <30% predicted), consider extubation to noninvasive assisted ventilation and postoperative chest physiotherapy (eg cough-assist)

is detected, radiographic assessment should also be performed [3]. Patients should also be routinely monitored for vertebral fractures starting at diagnosis and upon the onset of glucocorticoid treatment [38].

Fracture prevention is critical, primarily because of patients' low bone density, starting in the ambulatory stage. Families should be instructed to remove obstacles in the home settings, and patients using a wheelchair outside of the home should be reminded to use a seatbelt since falls out of a wheelchair are a common cause of lower extremity fractures in people with DMD, and caregivers should be taught how to transfer patients safely [3]. Patients who do experience acute lower extremity fracture/trauma should be monitored for fat emboli [39,40]. Operative fixation for long bone fractures can benefit from early mobilization and range of motion, particularly for hip and femoral shaft fractures (Fig. 2). Most other fractures can be treated with closed reduction and cast immobilization [3].

Early nonambulatory stage

In the early nonambulatory stage, contracture management continues to be critical to preserve function. An occupational therapist should assist with upper extremity stretching to prevent contractures, and resting night hand splint use may also be beneficial in preventing contractures [39,41]. An emphasis should be placed on managing hip and knee contractures to improve wheelchair positioning and supported standing [3]. Surgical intervention for hip and knee contractures should only be used to alleviate symptoms since correction is unlikely to be achieved [3]. Surgical intervention for the foot and ankle should only be performed if requested to help with wheelchair positioning or shoe wear or if the family is committed to continuing supported standing for health benefits, including prevention of contracture progression, improved bone health, and improved pulmonary toilet [3].

Spine management in the early nonambulatory stage is more involved than in the ambulatory stage. The standard usage of glucocorticoids has decreased the development of scoliosis requiring surgical intervention, though the etiology of this protective factor of glucocorticoids is unclear [42]. Nevertheless, clinical physical examination should always include a spine inspection for curvatures, including scoliosis and lordosis (Fig. 3) [42]. A spine radiograph may be obtained upon a patient initially

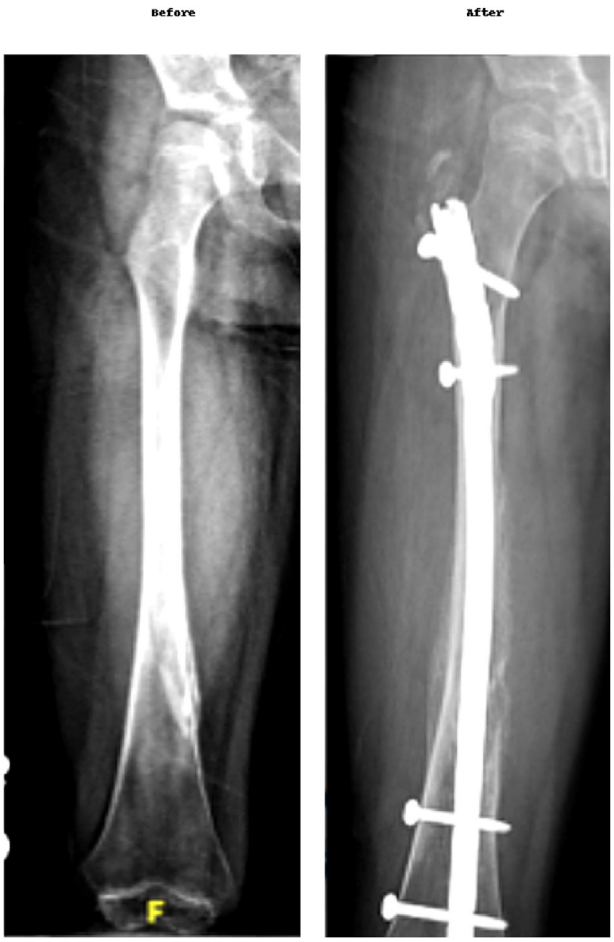

Figure 2. Anteroposterior radiographs from before and after fixation for a 12-year-old male with Duchenne muscular dystrophy who sustained a femur fracture during a ground-level fall.

Figure 3. Hyperlordosis in a 14-year-old male with Becker's muscular dystrophy prior to spinal fusion.

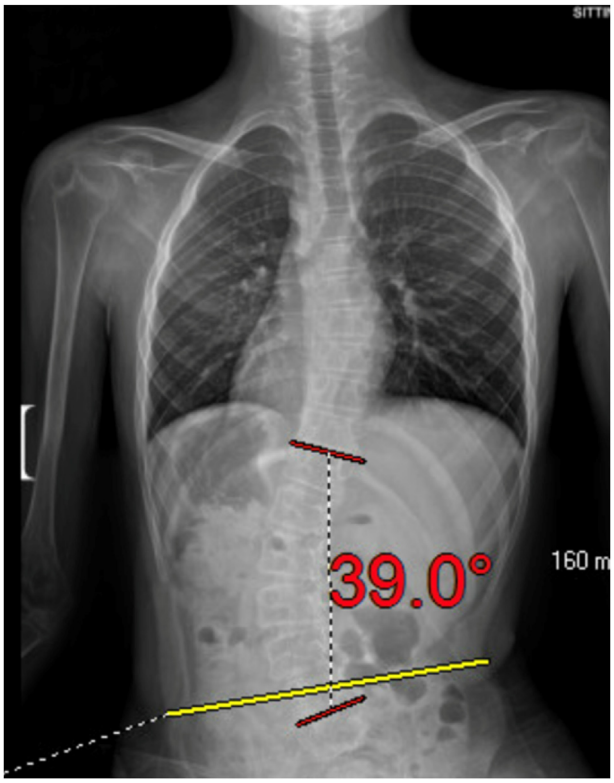

Figure 4. Preoperative anteroposterior radiograph of a 13-year-old male with Duchenne muscular dystrophy with 39° of scoliosis and 10° of pelvic obliquity.

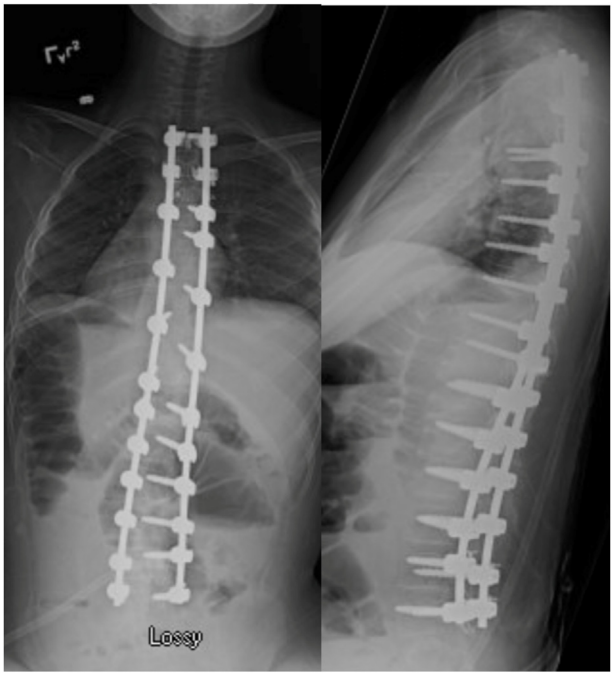

Figure 5. Postoperative anteroposterior and lateral radiographs of a 13-year-old male with Duchenne muscular dystrophy with 39° of scoliosis and 10° of pelvic obliquity who underwent posterior spine fusion from T2 to L5.

becoming non-ambulatory to allow for a more accurate comparison to measure future change and progression [3]. Patients with a spinal curve of 20° or more should be referred to an orthopaedic surgeon [3]. All patients should receive lateral supports in wheelchairs to help with functioning and positioning [42].

Late nonambulatory stage

A patient who has reached the late nonambulatory stage commonly has fixed hip and knee contractures, equinovarus contractures at the ankle, and upper extremity contractures [3]. Surgical intervention can be considered for pain, positioning problems, or skin integrity concerns [3].

Yearly seated scoliosis radiographs should be performed [3]. In patients for whom a progressive curve is a concern, posterior spinal fusion is recommended to optimize comfort and function (Figs. 4 and 5) [3]. While considerations should be patient-specific, one cohort study (n = 199) comparing surgical vs nonsurgical management of scoliosis in patients with DMD found that surgery led to an improved forced vital capacity for two years postoperatively and subsequently led to prolonged survival [43]. While there is conflicting evidence on when to intervene, it is accepted that in prepubertal patients, not on glucocorticoids and at a high risk of rapid deterioration, surgery should be performed once the curve has progressed beyond 20° [44]. Some authors recommend fusion to the pelvis in patients with greater than 15° of pelvic obliquity [3]. Others suggest fusion to L5 may be reasonable to maintain some movement at the pelvis [45]. A change in practice has resulted from the widespread use of glucocorticoids among patients with DMD, thereby resulting in slower progression of curves. For patients who are nearing puberty and on glucocorticoid therapy, guidelines are less clear and are more focused on functional status and comfort [46]. Some recent evidence favors a "watchful waiting" approach, such that curves under 45° are followed for cardiopulmonary function changes and operated on at later stages [47]. Regardless of whether surgical intervention is utilized, seating should be optimized to achieve maximal comfort [3].

Important social considerations

It is imperative to attend to the psychosocial needs of patients with DMD and their families for many reasons. Many parents report that the stress caused by psychosocial problems faced by their child exceeds the stress that is associated with the physical aspects of their child's condition [48]. Providers should ensure that families have access to social services, psychotherapy, social interaction interventions (peer education, modified sports), educational interventions, and care/support interventions (home healthcare services, transition planning) [1]. Providers may also connect families with advocacy groups, including the Muscular Dystrophy Association and the Parent Project Muscular Dystrophy.

Finally, providers may establish a multidisciplinary clinic for patients with DMD at their institution or connect families with these clinics at other institutions. Multidisciplinary care has led to improved survival of patients, likely a result of improved communication between specialists, leading to measures taken for prevention, early identification, and treatment of potentially modifiable complications [21]. A comprehensive multidisciplinary team should provide neuromuscular, rehabilitation, endocrine, gastrointestinal, nutritional, respiratory, cardiac, bone health, orthopaedic, psychosocial, and transition management [21].

Novel treatments

Glucocorticoid therapy has proven benefits on ambulatory status, pulmonary function, and life expectancy [49,50]. However, prolonged glucocorticoid therapy is associated with severe adverse effects. The development of targeted therapies is a challenge, given that thousands of unique mutations have been identified in the DMD gene [51]. Newly approved therapies for the treatment of DMD can be referenced in Table 3 [52–54]. Patients' genetic mutations and/or age define eligibility criteria for these novel treatments.

Indeed, these novel treatments, which will prolong lifespan and improve quality of life, are likely to change the way we treat patients with DMD significantly. Though it is difficult to predict what the future of orthopaaedic treatment for DMD holds, it may mirror recent changes in treatment for spinal muscular atrophy (SMA).

Table 3.
Eligibility criteria for use of novel treatments for Duchenne muscular dystrophy.

Treatment class	Treatment name	Eligibility criteria
Antisense oligonucleotide	Casimersen	Patients with a mutation of the DMD gene amenable to exon 45 skipping
Adeno-associated virus vector-based gene therapy	Delandistrogene moxeparvovec	Ambulatory patients aged 4 through 5 years with a confirmed mutation in the DMD gene, but with no deletion in exon 8 and/or exon 9 in the DMD gene
Glucocorticoid	Deflazacort	Patients 2 years of age and older
Antisense oligonucleotide	Eteplirsen	Patients with a mutation of the DMD gene amenable to exon 51 skipping
Antisense oligonucleotide	Viltolarsen	Patients with a mutation of the DMD gene amenable to exon 53 skipping
Antisense oligonucleotide	Golodirsen	Patients with a mutation of the DMD gene amenable to exon 53 skipping
Histone deacetylase enzyme inhibitor	Givinostat	Patients 6 years of age and older

Summary

Orthopaedic surgeons play a critical and dynamic role in the management of patients with DMD. As patients progress from ambulators to nonambulators, the goals of orthopaedic care change from mobility-preserving to comfort-based. Fracture prevention is crucial in prolonging ambulation and requires close monitoring of bone mineral density and mitigation of potential underlying endocrinopathies. As novel gene therapy treatments emerge with the potential to prolong ambulation, orthopaedic surgeons will become increasingly essential in preserving function and improving quality of life for patients with DMD.

Ethics approval and consent

Approval not required for this study. This study does not involve human subjects.

Author Contributions

Uma Balachandran: Writing – review & editing, Writing – original draft, Conceptualization. **Taylor Mustapich:** Writing – review & editing, Conceptualization. **Sheena C. Ranade:** Writing – review & editing, Supervision.

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Declarations of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jposna.2024.100154.

View the videos on POSNAcademy here: Video 1: http://www.kaltura.com/tiny/lgukj. Video 2: http://www.kaltura.com/tiny/elx46.

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