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Pediatric Neurology (Harvey Singer, Section Editor)

Autoimmune Neuromuscular Disorders in Childhood

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Opinion statement

Autoimmune neuromuscular disorders in childhood include Guillain-Barré syndrome and its variants, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), juvenile myasthenia gravis (JMG), and juvenile dermatomyositis (JDM), along with other disorders rarely seen in childhood. In general, these diseases have not been studied as extensively as they have been in adults. Thus, treatment protocols for these diseases in pediatrics are often based on adult practice, but despite the similarities in disease processes, the most widely used treatments have different effects in children. For example, some of the side effects of chronic steroid use, including linear growth deceleration, bone demineralization, and chronic weight issues, are more consequential in children than in adults. Although steroids remain a cornerstone of therapy in JDM and are useful in many cases of CIDP and JMG, other immunomodulatory therapies with similar efficacy may be used more frequently in some children to avoid these long-term sequelae. Steroids are less expensive than most other therapies, but chronic steroid therapy in childhood may lead to significant and costly medical complications. Another example is plasma exchange. This treatment modality presents challenges in pediatrics, as younger children require central venous access for this therapy. However, in older children and adolescents, plasma exchange is often feasible via peripheral venous access, making this treatment more accessible than might be expected in this age group. Intravenous immunoglobulin also is beneficial in several of these disorders, but its high cost may present barriers to its use in the future. Newer steroid-sparing immunomodulatory agents, such as azathioprine, tacrolimus, mycophenolate mofetil, and rituximab, have not been studied extensively in children. They show promising results from case reports and retrospective cohort studies, but there is a need for comparative studies looking at their relative efficacy, tolerability, and long-term adverse effects (including secondary malignancy) in children.

Introduction

Childhood autoimmune neuromuscular diseases are a heterogeneous group of acquired inflammatory disorders that result from autoimmune sensitization. The most common ones include Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), juvenile myas-

thenia gravis, and juvenile dermatomyositis. Others, such as vasculitic neuropathies, Lambert-Eaton myasthenic syndrome, polymyositis, and overlap myositis, have been reported in children but are rare in this age group.

These diseases share some common elements of immune dysregulation, namely T-cell activation with subsequent antibody and complement deposition in nerve, neuromuscular junction, or muscle (Table 1). Postinfectious molecular mimicry and genetic predispositions have been proposed for some autoimmune disorders, although mechanistic details remain unclear. Treatment of childhood autoimmune disorders is based upon published prospective and retrospective cohort studies, expert opinion, pediatric randomized controlled trials (particularly for Guillain-Barré syndrome and dermatomyositis), and extrapolation of results from adult studies. Early diagnosis and initiation of treatment can significantly reduce long-term morbidity for these diseases.

Outcome is often good when aggressive and appropriate therapies are used to treat these disorders, but some of the treatments used have not been studied as rigorously in children as in adults. Further prospective studies of therapies for these diseases in childhood are needed.

Treatment

Guillain-Barré syndrome

- Guillain-Barré syndrome (GBS) results from a loss of immunologic tolerance wherein autoreactive T lymphocytes, antibodies, and complement damage myelinated peripheral nerves [1]. Two thirds of GBS patients have an antecedent infection in the month prior to onset, fueling the theory of postinfectious molecular mimicry as the basic pathophysiologic mechanism [2]. GBS is uncommon in the first few years of life, but rare cases of neonatal GBS have been reported [3]. GBS is divided into several clinical subgroups: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller-

Table 1. Antibodies in autoimmune neuromuscular disorders of childhood

Disorder	Antibody[a]
Neuromuscular junction	
Juvenile myasthenia gravis (JMG)	Anti-AChR, anti-MuSK, anti-striated muscle
Lambert-Eaton myasthenic syndrome (LEMS)	Anti-VGCC
Muscle	
Dermatomyositis, polymyositis	Myositis-specific antibodies Anti-Jo1, anti-p155, anti-p140 Anti-nuclear antibody (ANA)
Nerve	
Guillain-Barré syndrome	
Acute inflammatory demyelinating polyneuropathy (AIDP)	None known
Acute motor axonal neuropathy (AMAN)	Anti-GM1
Miller-Fisher variant	Anti-GQ1b
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Anti-MAG (rare)

[a]Positive antibody titers are not always identified in patients with these disorders, so the sensitivity of the specific titer should be considered when interpreting such results

Fisher syndrome (MFS), and acute motor axonal neuropathy (AMAN). Treatment is similar for all forms of GBS.

- Pediatric and adult GBS patients present with progressive, symmetrical muscle weakness and diminished or absent deep tendon reflexes. Pain is often a prominent symptom, particularly in younger children, with 50% to 80% complaining of severe back, buttock, or limb pain [4–6, 7••]. Autonomic symptoms, including variability in heart rate, blood pressure, and thermoregulation, occur in 20% to 40% of children, with respiratory failure seen in 16% to 17% [4, 5]. Both autonomic and respiratory complications are less frequent in children than in adults. Children presenting with symptoms suggestive of GBS require close observation because of the possibility of rapidly progressive respiratory weakness, bulbar dysfunction, or autonomic dysfunction.
- Diagnostic criteria are well established for GBS [8]. In recent years, enhancement and thickening of the nerve roots on MRI imaging of the spine have been used to support the diagnosis, but these findings are not always specific to GBS [9•]. The long-term outcome of childhood GBS is quite favorable, though recovery is sometimes prolonged in the AMAN subtype, compared with AIDP [10]. Young age and rapid symptom progression may heighten the risk of long-term sequelae, but even though over 20% of children experience residual weakness, it rarely results in any functional impairment [4].
- Early treatment with intravenous immunoglobulin (IVIG) or plasma exchange (PE) is recommended for any child with GBS who has difficulty ambulating [11].

Intravenous immunoglobulin (IVIG)

Two small, randomized pediatric trials have demonstrated the efficacy of early IVIG therapy versus placebo [12, Class II] and versus late IVIG treatment [13, Class II]. In each study, IVIG reduced the time between symptom onset and the patients' initial and complete recovery [12, 13]. A retrospective study also supports the use of IVIG in pediatric GBS [14, Class IV].

Standard dosage The total IVIG dose is typically 2 g/kg divided over 2 to 5 days.

Mechanism of action Multiple actions have been postulated. IVIG has been shown to neutralize the blocking effects of some autoantibodies [15]. IVIG is also thought to downregulate T-cell activity and antibody production.

Side effects Headache, nausea, vomiting, allergic reactions, and aseptic meningitis may occur. IVIG must be used cautiously in children with cardiac or renal dysfunction. Renal failure has been described in rare cases.

Cost IVIG is very expensive.

Plasma exchange

PE, also known as plasmapheresis, is an accepted alternative to IVIG therapy in GBS patients. PE appears as efficacious as IVIG in at least five adult randomized controlled trials [16, Class I]. PE has also been shown to improve patient strength and reduce duration of mechanical ventilation more than placebo in adult GBS, although these studies were subject to less

rigorous design [11, Class II]. There is one case–control study of PE in childhood GBS [17, Class III]. No pediatric randomized controlled trial has studied the efficacy or tolerability of PE in this population. On the basis of the strong evidence of equal efficacy of IVIG and PE for adult GBS patients, either therapy can be offered to pediatric GBS patients. The choice between the two treatments in a particular case may be influenced by technical feasibility, side effect profile, and cost.

Mechanism of action PE is thought to wash out or remove autoantibodies and inflammatory cytokines.

Main side effects Potential short-term side effects include hypotension, electrolyte imbalance, or coagulopathy. Chronic PE frequently causes anemia, and it also may cause hypocalcemia and hypogammaglobulinemia (with increased susceptibility to infection) [18].

Corticosteroids and other immunosuppressive medications

Corticosteroids are not beneficial in the treatment of GBS [19, Class II]. Given the short, monophasic nature of GBS, there is no role for chronic immunosuppressive medications.

Physical therapy and exercise

Physical therapy is essential in the rehabilitation of children with GBS. This intervention can help a child regain skills during convalescence and may also help prevent the formation of contractures.

Chronic inflammatory demyelinating polyradiculoneuropathy

- CIDP is distinguished from GBS by the chronic nature of the disease. Children demonstrate either a progressive or relapsing sensorimotor polyneuropathy and/or polyradiculopathy for at least 2 months [20]. Although many CIDP patients exhibit a slow, insidious onset of weakness and sensory loss, up to 16% may exhibit an initial acute onset that mimics GBS [21].
- CIDP diagnostic criteria are aimed at distinguishing the disorder both from its acute-onset counterpart, GBS, and from hereditary and metabolic neuropathies [20, 22, Class IV]. Diffuse nerve root thickening and gadolinium enhancement on spine MRI were present in 60% of adult CIDP patients in one series [23]. These findings have also been observed in childhood CIDP [24] and can strengthen diagnostic certainty when present, but it should be noted that similar MRI findings may be seen in inherited neuropathies such as Charcot-Marie-Tooth disease [25, Class IV].
- CIDP may be treated with IVIG, PE, or corticosteroids [26••, Class I].

Diet and lifestyle

Adequate intake of vitamin D and calcium is essential for optimizing bone health and reducing risk of osteoporosis. Recommendations for vitamin D supplementation vary, but a dose of 800 to 1000 IU daily is reasonable. Calcium intake should be optimized primarily from dietary sources.

Growth velocity and weight gain should be closely monitored, par-

ticularly in children receiving corticosteroids. These recommendations are relevant to all autoimmune neuromuscular disorders of childhood.

IVIG and PE

Several case series of childhood CIDP have reported IVIG and corticosteroids to be efficacious [24, 27–32, Class IV]. PE also appears to be beneficial in some cases of childhood CIDP, though it is less frequently used [24, 28, 31, 32, Class IV]

Numerous randomized trials of adult CIDP have shown IVIG to be superior to placebo [33–37, Class I]. PE has also been demonstrated to be superior to placebo in adult CIDP [38]. Other trials demonstrated equal efficacy of IVIG versus PE [39, Class I] or corticosteroids [40, Class I].

Corticosteroids

Corticosteroids appear to be effective in adults [40, Class I] and children [24, 27–29, 31, 32, Class IV] with CIDP.

Mechanism of action Corticosteroids exert a broad immunosuppressive effect; the function and numbers of lymphocytes and monocytes are particularly affected [41].

Main side effects The numerous side effects of chronic corticosteroid therapy [42] are particularly detrimental to children who are at a critical stage of vertical growth and bone mineral deposition. In rare cases, the initiation of steroids has been linked to hip osteonecrosis. Potential complications from long-term corticosteroid therapy can include decreased linear growth velocity and reduction of final adult height, bone demineralization, weight gain, acne, and behavior problems. Hypertension, hyperglycemia, and cataracts may occur.

Special points Depending on the severity of the case and the expected duration of treatment, a steroid-sparing drug (e.g., azathioprine) may be started simultaneously, with the goal of reducing the duration of steroid treatment.

Azathioprine

Azathioprine is the most widely used steroid-sparing therapy in childhood CIDP [27, Class IV]. One prospective cohort study of azathioprine in adult CIDP failed to show any definite improvement when this medication was added for patients receiving corticosteroids [43, Class II], but this study may have been too short (9 months) to detect beneficial effects.

Standard dosage A standard starting dose for azathioprine is 1 mg/kg per day given daily or divided in two doses. The dose may be increased by 0.5 mg/kg per day every 4 weeks to a maximum of 2.5 mg/kg per day. Dose adjustments are needed in renal failure and thiopurine methyltransferase deficiency. Dosing by weight may need to be lower in obese patients who weigh more than the typical adult. A trial of 12 weeks is usually sufficient to determine therapeutic efficacy.

Mechanism of action Azathioprine antagonizes purine metabolism inhibiting DNA and RNA replication.

Main side effects Side effects can include somnolence, bone marrow suppression, and reversible hepatitis or pancreatitis. Surveillance blood testing is required. Female patients should be counseled about possible teratogenic effects of this and other immunosuppressants. There have been reports of malignancy associated with chronic azathioprine use [44, Class IV]. The US Food and Drug

Administration (FDA) has warned that there is a risk of fatal hepatosplenic T-cell lymphoma in adolescents and young adults receiving this therapy. These risks should be discussed with any patient before the initiation of treatment and again during treatment. Alternative therapies should be discussed as needed, especially when the duration of azathioprine use extends beyond a year.

Other immunosuppressants

Cyclosporine (discussed below) offered some benefit in an adult CIDP trial [45, Class III] and in a small series of children [46, Class IV].

Case reports and retrospective trials have looked at other immunosuppressant medications, but data pertaining to their efficacy in children is sparse.

Physical therapy and exercise

Physical therapy is an important component of the long-term management of CIDP. This intervention may help children, especially in the recovery phase of exacerbations, and also may help to prevent contractures.

Juvenile myasthenia gravis

- Patients with juvenile myasthenia gravis (JMG) can be offered three main categories of disease-modifying therapy: acetylcholinesterase inhibitors (AChE-I), medical immunomodulation or immunosuppression, and surgical intervention (thymectomy).

Diagnosis

- JMG is an autoimmune disorder resulting from antibodies directed at neuromuscular junction proteins, most commonly acetylcholine receptors (AChR). Children develop symptoms of muscle fatigability due to impaired neuromuscular transmission. Prepubertal patients often present with isolated oculomotor symptoms, including diplopia and ptosis [47, Class IV]. Some children go on to develop generalized weakness, though this appears to occur less frequently than in post-pubertal patients. No clear gender predominance exists in prepubertal JMG patients [48, Class IV], but a female preponderance emerges after puberty [49, 50, Class IV]. JMG can present at any age but is less common during infancy. In infants and toddlers, JMG may be difficult to differentiate from transient neonatal myasthenia gravis and congenital myasthenic syndrome.
- Although the diagnosis of JMG is based primarily upon the clinical presentation, supportive data include the presence of serum antibodies, edrophonium testing, and abnormal electrodiagnostic testing (repetitive nerve stimulation and single-fiber electromyography [EMG]).
- Whereas antibodies to the nicotinic AChR are found in 80% of adults with myasthenia gravis [51], only 50% of prepubertal and 70% of peripubertal JMG patients have anti-AChR antibodies [49, 52, Class

IV]. Antibodies to muscle-specific kinase (MuSK) and to striated muscle have been reported in children but are rare in JMG, and the cost of anti-MuSK titers is often higher than that of AChR antibody titers [53•, 54].

- Edrophonium testing involves the use of a short-acting AChE-I. Dosing in infants should be discussed with a neurologist experienced with performing the test in this age group. Children older than 1 year who weigh less than 34 kg are treated with an edrophonium test dose of 0.5 mg, followed by 1-mg increments to a maximum total dose of 5 mg. Children weighing 34 kg or more are treated with the adult edrophonium dose, a 0.5-mg test dose followed by increments of 1 to 2 mg until a maximum dose of 10 mg is attained. In addition to clinical monitoring, preinjection and postinjection photos, taken with the consent of the patient and/or family, may be helpful. Because of the risk of symptomatic bradycardia, asystole, and hypotension, testing must be performed in a monitored setting with staff trained in cardiac resuscitation. Some patients with congenital myasthenic syndrome may deteriorate with exposure to an AChE-I (e.g., *COLQ* mutation or AChR slow channel mutation). Positive edrophonium testing is not specific for JMG and can be seen with other disorders of neuromuscular transmission. Lambert-Eaton myasthenic syndrome (LEMS) has been reported in children but is exceedingly rare in this age group [55].
- Young children may require sedation to facilitate repetitive stimulation and stimulated single-fiber EMG.

Diet and lifestyle

Adequate intake of vitamin D and calcium is essential for optimizing bone health and reducing risk of osteoporosis. Recommendations for vitamin D supplementation vary, but a dose of 800 to 1000 IU daily is reasonable. Calcium intake should be optimized primarily from dietary sources.

Growth velocity and weight gain should be closely monitored, particularly in children receiving corticosteroids.

Pharmacologic therapy

Pyridostigmine

Pyridostigmine bromide is standard first-line JMG therapy.

Standard dosage Initial oral dosing is 0.5 to 1 mg/kg per dose (maximum 60 mg) every 4 to 6 h while awake. Onset of effect occurs rapidly (within 15–30 min) and duration is up to 3 to 4 h. For young children, regular tablets may be crushed or the liquid form (60 mg/5 mL) can be used. The maximum daily dose is 7 mg/kg per day or 300 mg/day. In rare cases, higher doses may be used, but only if prescribed by a neurologist experienced with this medication. The

	intravenous form of pyridostigmine requires a significant dose adjustment, so it should be used with caution, if at all.
Drug interactions	Pyridostigmine may increase the effects of depolarizing neuromuscular blocking drugs (e.g., succinylcholine, aminoglycosides) and β-blockers. Corticosteroids may lessen the effects of pyridostigmine. Atropine is an antagonist.
Main side effects	Muscarinic (cholinergic) effects (e.g., cramping, diarrhea, salivation) may limit dosing in some children. Overdosage may precipitate a cholinergic crisis, which can be difficult to distinguish from a myasthenic crisis except for superimposed muscarinic symptoms, which may not be obvious in every patient.

Intravenous immunoglobulin

	IVIG is commonly used to treat acute JMG exacerbations and also is used as chronic maintenance therapy for some patients. Data pertaining to IVIG efficacy in myasthenia gravis (MG) is based largely on data from adult randomized placebo-control trials [56, Class I].
Standard dosage	Acute JMG exacerbations are treated with 2 g/kg of IVIG, divided over 2 to 5 days [53•]. The precise dose of IVIG remains unclear, with an adult study documenting no short-term difference in efficacy between 1 g/kg versus 2 g/kg [57, Class I]. Anecdotally, some patients can be maintained on chronic IVIG therapy (typically 1 g/kg every few weeks, with the exact interval depending on severity), but there are no randomized studies supporting this approach [58].
Mechanism of action	Multiple actions have been postulated. IVIG has been shown to neutralize the blocking effects of some autoantibodies [15]. IVIG is also thought to downregulate T-cell activity and antibody production.
Side effects	Headache, nausea, vomiting, allergic reactions, and aseptic meningitis may occur. IVIG must be used cautiously in children with cardiac or renal dysfunction. Renal failure has been described in rare cases.
Cost	IVIG is very expensive.

Corticosteroids

	Corticosteroids (prednisone, prednisolone, methylprednisolone) are effective immunosuppressants with good evidence for their efficacy in MG [59, Class II]. Steroid therapy is a traditional choice for MG patients requiring long-term immunosuppression [60•, Class IV]. Several studies have demonstrated a beneficial response in more than 70% of adult MG patients [61–64; Class IV].
Standard dosage	Caution must be taken when initiating therapy, as increased weakness may occur within the first 1 to 2 weeks of treatment, potentially precipitating a myasthenic crisis [61]. To minimize this risk, outpatient corticosteroid therapy should be started at a low dose (typically 0.5 mg/kg per day; maximum 30 mg/day) and gradually increased at weekly increments until an effect is observed [53•]. Severely ill patients who are admitted to the hospital may start at higher doses (intravenous methylprednisolone 2 mg/kg per day, with a maximum of 60–80 mg/day), but they need to be observed in the hospital for at least a week after initiation [53•].
Mechanism of action	Corticosteroids exert a broad immunosuppressive effect; the function and numbers of lymphocytes and monocytes are particularly affected [41].
Main side effects	The numerous side effects of chronic corticosteroid therapy [42] are particularly detrimental to children who are at a critical stage of vertical growth and bone mineral deposition. In rare cases, the initiation of

steroids has been linked to hip osteonecrosis. Potential complications from long-term corticosteroid therapy can include decreased linear growth velocity and reduction of final adult height, bone demineralization, weight gain, acne, and behavior problems. Hypertension, hyperglycemia, and cataracts may occur.

Special points Depending on the severity of the case and the expected duration of treatment, a steroid-sparing drug (e.g., azathioprine) may be started simultaneously, with the goal of reducing the duration of steroid treatment.

Cost Steroids are inexpensive, but they may cause significant and costly long-term side effects when used on a chronic basis.

Azathioprine

Azathioprine is commonly used as a steroid-sparing immunosuppressant agent in adult MG [65, Class IV] and JMG [48, 50, 53•, Class IV]. Although randomized trials in adult MG patients have not found azathioprine to improve clinical strength scores [66, Class I], it has been shown to be associated with lower corticosteroid dosing during long-term use by patients with chronic MG [67, Class I].

Dosage and side effects are similar to those in patients with CIDP, as discussed above.

Cyclosporine

Cyclosporine, also classified as a steroid-sparing immunosuppressant, has proven beneficial in adult MG [68, Class I; 69, 70, Class III], and its use has been reported in some JMG patients [50, Class IV].

Standard dosage Dosing of cyclosporine for JMG has not been established, but the dosing guidelines for inflammatory diseases may be a useful guide. These suggest a starting dose of 2.5 mg/kg per day divided in two doses. At 8 and 12 weeks of therapy, the dose may be increased by 0.5 to 0.75 mg/kg per day. The maximum dose is 4 mg/kg per day. The dosage may need to be adjusted for renal or hepatic impairment. Different brands of cyclosporine are not bioequivalent, so each patient must stay on the same brand for the duration of therapy. Checking serum levels and monitoring for signs of end-organ toxicity are essential. Neurologists not experienced in the use of cyclosporine in children should consult with a colleague who has such experience before initiating therapy.

Mechanism of action Cyclosporine inhibits the production and release of interleukin 2, thereby inhibiting T-cell activation.

Main side effects Adverse effects may include abdominal pain, nausea, diarrhea, hepatitis, bone marrow suppression, hirsutism, and gingival hyperplasia. Serious potential effects include nephrotoxicity (often manifesting as hypertension), malignancy, and infections. Seizures infrequently occur (particularly if receiving concomitant high-dose corticosteroids). These side effects must be discussed with patients and their families before initiation of treatment. Breast-feeding is contraindicated during therapy.

Drug interactions Cyclosporine is metabolized via the cytochrome P450 pathway, giving rise to many potential drug interactions.

Tacrolimus

Tacrolimus therapy appeared promising in one small, unblinded, randomized trial [71, Class II] and one nonrandomized trial in adult MG

patients [72, Class III]. Tacrolimus has been used for other pediatric diseases such as severe atopic dermatitis and in children who have received solid-organ transplants. There are no data pertaining to the use of this drug in JMG, so a physician experienced in its use should be consulted prior to the initiation of therapy. Blood testing is required to determine therapeutic levels and monitor for signs of end-organ toxicity.

Mechanism of action Tacrolimus affects intracellular calcineurin, inhibiting T-cell activation.

Main side effects Adverse effects can include nausea, diarrhea, bone marrow suppression, hypertension (nephrotoxicity), neurotoxicity (encephalopathy, polyneuropathy), ototoxicity, and increased risk of malignancy.

Drug interactions Concomitant use with other immunosuppressants can increase risk of infection and secondary malignancy. Concomitant use with cyclosporine may increase the risk of nephrotoxicity. Tacrolimus is metabolized via the cytochrome P450 pathway, giving rise to many potential drug interactions. Grapefruit may increase the serum tacrolimus concentration.

Other immunosuppressants

Methotrexate is often used as an alternative immunosuppressant agent in adults with MG who are unable to tolerate azathioprine, although very little published evidence supports the use of this drug in MG. The proven efficacy of methotrexate for other autoimmune diseases (such as dermatomyositis, discussed below) is used as the main argument for the use of this drug in MG.

Cyclophosphamide therapy has been used for severe, treatment-resistant adult MG [65, Class IV].

Rituximab has been used with promising results in adults with severe, refractory MG [73, Class IV], although the efficacy of this drug in JMG is unclear.

There are a number of anecdotal reports of the efficacy of mycophenolate mofetil in adult MG, but a large randomized controlled trial in adults failed to show a clear benefit [74, Class I]. Thus its role in MG therapy is unclear at this time.

Plasma exchange

- PE is an alternative to IVIG for treating acute exacerbations [18, Class I] (typically with five exchanges performed on alternate days) or chronic JMG (typically one exchange every few weeks) [53•], although no randomized trials support the long-term use of PE in this population. IVIG and PE show equal short-term efficacy in treating exacerbations of adult MG [18, Class I; 75•, Class I]. PE also has been shown to be beneficial when administered to adults with MG prior to thymectomy, reducing the duration of postoperative mechanical ventilation [76•, Class II].
- Potential short-term side effects of PE include hypotension, electrolyte imbalance, or coagulopathy. Chronic PE frequently causes anemia, and it also may cause hypocalcemia and

hypogammaglobulinemia, with increased susceptibility to infection [18].

Surgical therapy

- Thymectomy is often performed in patients with generalized MG, including children. The presence of a thymoma is an absolute indication for thymectomy. Based on retrospective data, thymectomy also appears to be beneficial for nonthymomatous generalized JMG, with almost 70% of patients improving after thymectomy and 40% exhibiting complete remission, including discontinuation of medication [77••, Class III]. These outcomes are better than the overall spontaneous remission rate of 14% to 30% in JMG [78, 79, Class IV]. Two retrospective studies also report an association between early thymectomy and likelihood of remission in JMG [77••, 78, Class IV]. These studies support the role of thymectomy as a therapy for JMG. Prospective data would be helpful, but conducting such a study would be difficult.

Physical therapy and exercise

- MG is one of the only neuromuscular disorders in which physical therapy and exercise should be used with caution. Excessive physical activity will often trigger worsening of symptoms. Physical therapy should be initiated only upon the recommendation of the treating neurologist, and is usually most helpful in the later stages of recovery or in the postoperative period after thymectomy. Light to moderate exercise is often beneficial, but only as tolerated by the patient.

Dermatomyositis

- Juvenile dermatomyositis (JDM) accounts for at least 85% of inflammatory myopathies in childhood [80]. JDM is a systemic disease resulting from desensitization of lymphocytes with subsequent damage mediated by autoantibodies and complement.
- Immunosuppressant therapy is the mainstay of JDM treatment and has brought about a marked improvement in long-term outcome with the advent of early and consistent treatment [81]. Mortality from JDM has decreased from 25% [81] to less than 2% [82]. Morbidity has also lessened, with one follow-up study reporting moderate to severe disability in less than 10% of children [82]. Treatment strategies in JDM are based on small, retrospective studies and expert opinion. There are no randomized controlled trials pertaining to JDM treatment.

Diagnosis

- Classically, the diagnostic criteria for dermatomyositis require patients to have a characteristic skin rash as well as any three of the following four additional features: symmetrical proximal muscle weakness, raised muscle enzyme levels, perifascicular atrophy on

muscle biopsy, or myopathic findings on EMG [83]. Most children will present with involvement of skin (90%) and/or muscle (>80%) [80, 84]. EMG is now performed for the diagnostic evaluation of dermatomyositis than less often than in the past, but it may be useful in cases of atypical presentations. Muscle MRI is a relatively new diagnostic tool that is becoming increasingly popular.

- Common muscle symptoms include myalgia and symmetrical weakness of the neck and hip flexors. When weakness precedes the characteristic skin findings, it may be difficult to distinguish JDM from other inflammatory myopathies (i.e., polymyositis, overlap myositis) or even some forms of muscular dystrophy.
- The characteristic skin findings of JDM include the heliotrope rash and Gottron papules (seen in 75% of patients) [84]. Other skin findings include malar rash, periungual telangiectasia, mouth ulcers, skin ulceration, and calcinosis.
- Organ systems less commonly involved include lungs (interstitial lung disease), gut (gastrointestinal bleeding), joints (arthralgia), heart (myocarditis), and eyes (cataracts).
- JDM is associated with autoantibodies in about 40% to 50% of cases [85, 86•]. Myositis-specific autoantibodies such as anti-Jo-1, anti-p155, and anti-p140 are the most common autoantibodies seen in JDM [86•]. An elevation of antinuclear antibodies (ANA), serum creatine kinase (CK), or erythrocyte sedimentation rate (ESR) is also found in many, though not all, children with active JDM [87].
- Adult dermatomyositis is typically associated with malignancy, but this is rare in JDM, and screening for occult malignancy is not necessary unless clinical suspicion exists [85, Class IV].

Diet and lifestyle

Adequate intake of vitamin D and calcium is essential for optimizing bone health and reducing risk of osteoporosis. Recommendations for vitamin D supplementation vary, but a dose of 800 to 1000 IU daily is reasonable. Calcium intake should be optimized primarily from dietary sources.

Growth velocity and weight gain should be closely monitored, particularly in children receiving corticosteroids.

Pharmacologic therapy

Corticosteroids

Corticosteroids are used by most clinicians in the treatment of JDM. A recent North American practice survey of pediatric rheumatologists revealed that clinicians treat mild JDM with corticosteroid monotherapy (<10% of cases); combination corticosteroid and methotrexate (40%), or corticosteroid, methotrexate, and hydrochloroquine (35%). Severe JDM was often treated with combined corticosteroid, methotrexate, and IVIG therapy or corticosteroids and cyclophosphamide [88•, Class IV].

Standard dosage	Therapy may begin with either high-dose oral prednisone (2 mg/kg per day, maximum 60–80 mg/day) or pulse intravenous methylprednisolone (20–30 mg/kg per day, maximum 1 g/day for 5 days) In either case, daily oral prednisone is then continued at 2 mg/kg per day (maximum 60–80 mg/day) for 4 weeks before gradual tapering [89••, Class IV]. Early and aggressive corticosteroid therapy is associated with better disease outcome [90, Class IV].
Main side effects	The numerous side effects of chronic corticosteroid therapy [42] are particularly detrimental to children who are at a critical stage of vertical growth and bone mineral deposition. In rare cases the initiation of steroids has been linked to hip osteonecrosis. Potential complications from long-term corticosteroid therapy can include decreased linear growth velocity and reduction of final adult height, bone demineralization, weight gain, acne, and behavior problems. Hypertension, hyperglycemia, and cataracts may occur.

Methotrexate

	Combination therapy using methotrexate and a corticosteroid has been shown to improve long-term outcome and reduce corticosteroid-related side effects in JDM. [91, 92, Class II].
Mechanism of action	Methotrexate is a dihydrofolate reductase inhibitor, which causes depletion of folic acid and depletion of DNA precursors.
Main side effects	Adverse effects can include nausea, diarrhea, bone marrow suppression, alopecia, rash, cystitis, hepatitis, and nephropathy. Female patients should be counseled about the risk of teratogenicity.
Drug interactions	Penicillin and aspirin may increase methotrexate levels.

Hydroxychloroquine

	Hydroxychloroquine has also been used as a successful adjunct therapy for JDM [93, Class III] and is often started concomitantly with corticosteroids and methotrexate, particularly in mild JDM [88•].
Mechanism of action	Hydroxychloroquine interferes with leukocyte chemotaxis and complement-dependent antigen–antibody reactions.
Main side effects	Adverse effects can include nausea, diarrhea, bone marrow suppression, psychiatric symptoms, rash, photosensitivity, and hepatotoxicity.

Other immunosuppressants

	Severe or refractory JDM has been treated with IVIG [94, Class IV], cyclosporine [95, Class IV; 96, Class III], cyclophosphamide [97, Class IV], mycophenolate mofetil [98, Class IV], tacrolimus [99, Class IV], and rituximab [100, Class IV]. One small retrospective study has suggested that certain JDM patients may do well with IVIG and/or methotrexate therapy alone (i.e., no corticosteroids) [101•, Class IV], but this study must be interpreted with caution, particularly as corticosteroid therapy is accepted as the standard of care by most physicians [88•].

Physical therapy and exercise

- Physical therapy and exercise will often be helpful in JDM, but the level of potential activity may be limited when the weakness is severe.

Disclosure

H. McMillan: none; B. Darras: consulting fees from Isis Pharmaceuticals, Athena Diagnostics; P. Kang: none.

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