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## Topical Review

## Management Strategies for CLN2 Disease



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**ABSTRACT**

CLN2 disease (neuronal ceroid lipofuscinosis type 2) is a rare, autosomal recessive, pediatric-onset, rapidly progressive neurodegenerative lysosomal storage disorder caused by tripeptidyl peptidase 1 (TPP1) enzyme deficiency, and is characterized by language delay, seizures, rapid cognitive and motor decline, blindness, and early death. No management guidelines exist and there is a paucity of published disease-specific evidence to inform clinical practice, which currently draws upon experience from the field of childhood neurodisability. Twenty-four disease experts were surveyed on CLN2 disease management and a subset met to discuss current practice. Management goals and strategies are consistent among experts globally and are guided by the principles of pediatric palliative care. Goals and interventions evolve as the disease progresses, with a shift in focus from maintenance of function early in the disease to maintenance of quality of life. A multidisciplinary approach is critical for optimal patient care. This work represents an initial step toward the development of consensus-based management guidelines for CLN2 disease.

**Keywords:** CLN2 disease, neuronal ceroid lipofuscinosis type 2, late-infantile neuronal ceroid lipofuscinosis, late-infantile Batten disease, management, consensus, palliative care

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**Introduction**

CLN2 disease, or neuronal ceroid lipofuscinosis type 2 (OMIM 204500), is a pediatric-onset, autosomal recessive, neurodegenerative lysosomal storage disorder caused by deficient activity of the enzyme tripeptidyl peptidase 1 (TPP1) and characterized by language delay, seizures, ataxia, movement disorders, motor deterioration, dementia, blindness, and early death.<sup>1</sup> The condition is very rare, with estimates of incidence ranging from 0.15 per 100,000 live births in Portugal,<sup>2</sup> 0.46 per 100,000 live births in West Germany,<sup>3</sup> and 0.78 per 100,000 live births in the United Kingdom<sup>4</sup> to as high as 9.0 per 100,000 live births in Newfoundland,<sup>5</sup> and an estimated prevalence of 0.6–0.7 per million in Scandinavia.<sup>6</sup> Deficient TPP1 activity leads to intralysosomal accumulation of autofluorescent storage material and is associated with neuronal and retinal cell loss, but the pathophysiology remains poorly understood.<sup>1,7</sup> Treatment is currently limited to symptomatic and supportive care.

The classic late-infantile phenotype of CLN2 disease has a predictable clinical course marked by epilepsy and rapid psychomotor decline.<sup>8–10</sup> The most common initial symptoms are language delay and seizures, which typically begin to manifest between the ages of two to four years; often, language delay precedes the onset of seizures.<sup>1,8–12</sup> Affected children most commonly present with an unprovoked seizure, although febrile seizures have also been reported.<sup>11</sup> Other initial symptoms include prominent truncal and peripheral ataxia, behavioral disturbances, and other developmental delays. Seizures may be polymorphic (e.g., generalized tonic-clonic, myoclonic, atonic) and often become drug resistant.<sup>1,13,14</sup> Following the onset of seizures, a rapid deterioration in cognitive and motor functions ensues over two to three years, leading to loss of speech and loss of voluntary movement by age six years.<sup>8–10</sup> Movement disorders, including myoclonus, dystonia, and spasticity, develop. Myoclonus (epileptic and nonepileptic) is a major feature that can be particularly difficult to treat and can disrupt rest and sleep.<sup>1</sup> Children often have sleep disturbance<sup>15</sup> and behavioral symptoms. Visual impairment may

begin as early as age four years but is not usually apparent or troublesome until severe deterioration is evident, and children eventually become blind by age 7–10 years.<sup>1,8,11</sup> Children lose the ability to swallow and become gastrostomy tube dependent.<sup>1,9</sup> Hearing is typically spared. Death usually occurs by midadolescence.<sup>1</sup> Atypical phenotypes associated with earlier or later symptom onset, varied symptoms, and/or slower disease progression have also been reported<sup>16–24</sup> but still lead to neurodegeneration and premature death.

The management of CLN2 disease is complex. Patients require extensive multidisciplinary medical care due to the high symptom load and the rapid rate of functional decline, and families require extensive psychosocial support, yet no management guidelines currently exist for this condition. Moreover, the literature on managing the neuronal ceroid lipofuscinoses (NCLs) in general is sparse.<sup>13,25,26</sup> Guidance on the management of this complex disease is necessary to ensure that patients and families receive appropriate care and support and becomes especially critical as disease-modifying therapies become feasible.<sup>27,28</sup> With the objective of improving outcomes in CLN2 disease, this article provides a detailed review and discussion of the complications associated with this condition, describes specific strategies for their management, and presents a framework for comprehensive care. Due to the dearth of published evidence, much of the information and guidance presented here is based on the practices and opinions of clinicians and patient advocates with extensive knowledge and experience in CLN2 disease.

**Methods**

A review of the literature was conducted using PubMed, Embase, and Scopus databases to identify and gather relevant evidence on the management of CLN2 disease. Search terms used were: (“CLN2 disease” OR “neuronal ceroid lipofuscinosis type 2” OR “late-infantile neuronal ceroid lipofuscinosis” OR “late-infantile Batten disease” OR “Jansky-Bielschowsky disease”) AND (“management” OR “care”). Since no published articles specific to CLN2 disease management were available, articles containing information related to the management of the NCLs in general were evaluated. To gain insight into disease-specific management

strategies, 24 CLN2 disease experts (health care professionals and patient advocates) from eight countries completed an online survey comprising questions on multidisciplinary management of CLN2 disease, and a smaller group subsequently met to discuss current management practices. The experts were identified and selected based on the literature and/or on their experience and specialty. The medical specialties/subspecialties represented were neurology/pediatric neurology, pediatric palliative care, genetics, physical therapy, pediatric intensive care/pediatric cardiology, neurodisability, pediatric pain management, pediatrics, pediatric dietitian, ophthalmology, neuropsychology, and sleep medicine. The institutions represented by the experts include well-established referral centers for NCL disorders, and the experts collectively manage, or have managed or evaluated, over 120 patients with CLN2 disease. The survey and meeting were sponsored by BioMarin Pharmaceutical Inc.

### Optimal management relies on early diagnosis

Early diagnosis of CLN2 disease is critical to ensure optimal care for patients and families but is challenging primarily due to a lack of disease awareness and the non-specificity of initial presenting symptoms. The diagnostic evaluation of isolated language delay in an otherwise “normal” toddler is limited once hearing loss is ruled out, and gaining control of seizures may take precedence over determining their etiology, contributing to delays in diagnosis. In addition, symptoms such as ataxia may be misinterpreted as side effects of anticonvulsive medication initially. A delay of 2–3 years between symptom onset and diagnosis is common,<sup>29</sup> and some children may appropriately be referred for speech therapy or have treatment for epilepsy before diagnosis. Most patients are diagnosed around five years of age when substantial loss of function has already occurred.<sup>10</sup> Timely diagnosis facilitates early initiation of disease-specific care, reduces the risk of inappropriate medications, and enables families to make informed decisions as early as possible regarding the goals of care and family planning. New-onset unprovoked seizures in combination with a history of early language delay in a child aged 2–4 years should prompt suspicion of CLN2 disease.<sup>10,12</sup> A photoparoxysmal response to low frequency (1–2 Hz) intermittent photic stimulation on electroencephalography (EEG) can also be helpful in identifying affected children; in one retrospective study, EEG recordings of 63% of patients with CLN2 disease ( $n = 15$ ) demonstrated a time-locked response to 1 Hz photic stimulation consisting of bioccipital or, less frequently, generalized spike and wave discharges.<sup>30</sup> Additional findings to support a suspicion of CLN2 disease are cerebellar atrophy and periventricular white matter T2 hyperintensities on magnetic resonance imaging.<sup>31–34</sup>

Once clinical suspicion of CLN2 disease or an NCL disorder has been established, the patient should undergo biochemical testing. The recommended gold standard for definitive diagnosis of CLN2 disease is the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots), together with the detection of pathogenic mutations in each allele of the *TPP1* gene (also known as the CLN2 gene).<sup>35</sup> However, when it is not feasible to perform both analyses, either deficient TPP1 enzyme activity in leukocytes or fibroblasts or the detection of two pathogenic mutations in trans alone can be diagnostic for CLN2 disease.<sup>35</sup> While there is wide allelic heterogeneity with 116 causative mutations identified to date,<sup>36</sup> two

common mutations, c.509-1G>C, a splicing mutation, and c.622C>T, a nonsense mutation, account for most of the reported *TPP1* mutant alleles worldwide,<sup>18,37,38</sup> greatly facilitating genetic testing for CLN2 disease. Although molecular testing has largely limited the use of electron microscopy studies in the diagnostic process, ultrastructural findings of curvilinear bodies in tissue biopsies (e.g., skin) may have diagnostic value in regions where molecular testing is not readily available.

### General principles and goals of management

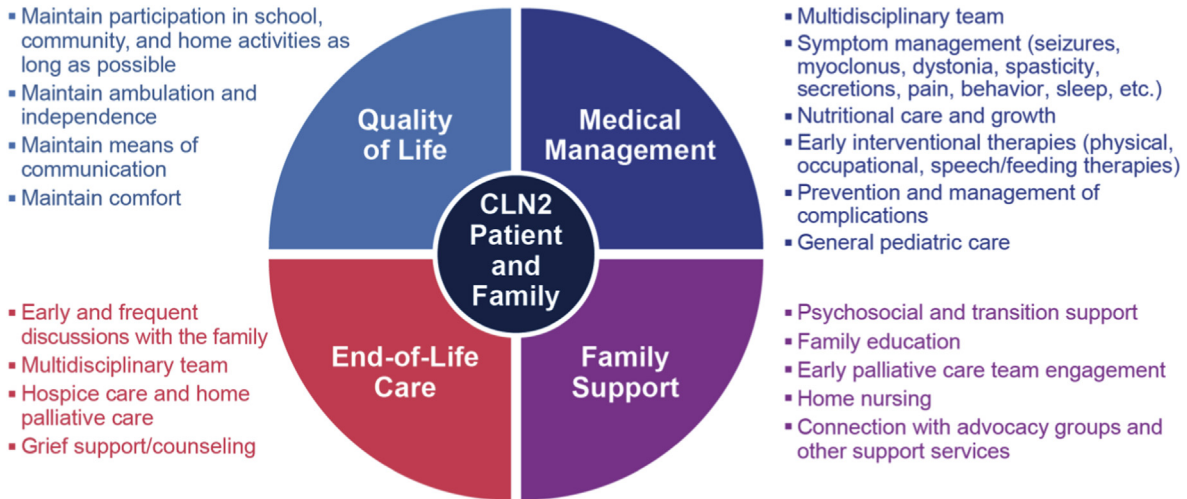
Management of CLN2 disease should be guided by the principles of pediatric palliative care,<sup>39–41</sup> a holistic approach to caring for children with complex medical needs. Optimizing the quality of life for patients and their families requires a multidisciplinary team of health care professionals, including physicians, nurses, therapists (i.e., physical, occupational, and speech), dietitians, psychologists, social workers, and counselors, working collaboratively to manage symptoms, minimize pain and suffering, and provide psychosocial and spiritual support. A supervising clinician (neurologist, palliative care specialist, or general pediatric specialist) typically oversees the coordination of care. Comprehensive care should be initiated as early as possible, ideally immediately after diagnosis. The best interests and values of patients and their families should be central in all decision-making processes. Frequent communication with families is important to ensure alignment of care goals and plans. [Figure 1](#) provides a framework for comprehensive patient- and family-centric care in CLN2 disease.

Goals and interventions will evolve as the disease progresses ([Figs 2 and 3](#)). During the early stage when children begin to manifest symptoms, effective management relies on early diagnosis and involves the establishment of a multidisciplinary care team, early implementation of disease-specific care, advance care planning with families, and family planning/genetic counseling. As the disease evolves beyond the initial presentation and the symptom burden increases, maintenance of function (particularly ambulation and communication) for as long as possible is the main goal of management. In the late stage of the disease, maintenance of the quality of life and the prevention of complications secondary to immobility and functional loss (e.g., decubitus ulcers, muscle atrophy, aspiration pneumonia) are the priorities of care. Optimal management of patients requires ongoing assessments and modification of treatment plans as needed. The frequency of clinic visits and assessments should be tailored to meet the individual needs of each child and family.

### Seizure management

Multiple seizure types are observed in CLN2 disease, including myoclonic, tonic, atonic, absence, and tonic-clonic.<sup>1,9</sup> As the disease progresses, myoclonic seizures can predominate. Drug management generally follows accepted principles for epilepsy.<sup>42</sup> Antiepileptic drugs (AEDs) are the mainstay of seizure management; common first-line options include valproate, benzodiazepines (clobazam/clonazepam), levetiracetam, and lamotrigine ([Table](#)). The overarching goal of seizure management is to achieve sufficient





**FIGURE 1.** A palliative care framework for CLN2 disease management facilitates comprehensive care of patients and their families. (The color version of this figure is available in the online edition.)

seizure control to support function (social interactions, mobility, fall prevention) while balancing the side effects (e.g., excessive sedation). The expert consensus is that seizure freedom is not a realistic goal; rather, the aims are to minimize the impact of seizures on the child’s well-being,

diminish the most disabling and life-threatening seizures, and maintain quality of life. Although polytherapy is often required because of the refractory nature of the seizures, it is important to use as few medications as possible to achieve satisfactory control. A combination of more than three to

	Early Stage	Rapidly Progressive Stage	Late Stage
Diagnostics	<ul style="list-style-type: none"> <li>• Urgency for early diagnosis</li> <li>• Suspect CLN2 disease in child with new-onset seizures + history of language delay/ataxia or other delays +/- PPR on 1-2 Hz IPS EEG +/- cerebellar atrophy, periventricular WM hyperintensities on brain MRI</li> <li>• Common misdiagnoses: non-specific language delay, non-specific epilepsy, myoclonic epilepsies</li> </ul>	<ul style="list-style-type: none"> <li>• Majority of children are diagnosed ~5 years of age (clinical suspicion is often late, not occurring until regression has occurred)</li> </ul>	<ul style="list-style-type: none"> <li>• Correct diagnosis is always important even if end-stage disease for clarity and genetic counseling</li> </ul>
Major Management Goals	<ul style="list-style-type: none"> <li>• Early diagnosis</li> <li>• Establish multidisciplinary care team</li> </ul>	<ul style="list-style-type: none"> <li>• Maintain function</li> </ul>	<ul style="list-style-type: none"> <li>• Maintain quality of life</li> </ul>
Medical Management	<ul style="list-style-type: none"> <li>• Symptom management</li> <li>• Periodic reassessment of medications</li> <li>• General pediatric care</li> </ul>	<ul style="list-style-type: none"> <li>• Symptom management</li> <li>• Ongoing assessments and modifications of treatment plans as needed</li> <li>• Reassessments of medications</li> <li>• General pediatric care</li> </ul>	<ul style="list-style-type: none"> <li>• Symptom management</li> <li>• Prevention of secondary complications</li> <li>• Ongoing assessments and modification of treatment plans as needed</li> <li>• Reassessments of medications</li> <li>• General pediatric care</li> </ul>
Quality of Life	<ul style="list-style-type: none"> <li>• Palliative care</li> </ul>	<ul style="list-style-type: none"> <li>• Palliative care</li> <li>• Maintain mobility and independence</li> <li>• Maintain means of communication</li> <li>• Maintain participation in school and community</li> </ul>	<ul style="list-style-type: none"> <li>• Palliative care</li> <li>• Maintain comfort</li> <li>• Maintain means of communication for as long as possible</li> <li>• Maintain participation in school and community for as long as possible</li> </ul>
End-of-life Care	<ul style="list-style-type: none"> <li>• Advance care planning with families</li> </ul>	<ul style="list-style-type: none"> <li>• Advance care planning with families</li> </ul>	<ul style="list-style-type: none"> <li>• Maximize comfort</li> <li>• Pain prevention and relief</li> <li>• Hospice care and home palliative care</li> </ul>
Family Support	<ul style="list-style-type: none"> <li>• Disease education</li> <li>• Family planning/Genetic counseling</li> <li>• Psychosocial support for parents, siblings, and other family members (grandparents)</li> <li>• Engagement with advocacy groups and other support services</li> <li>• Early palliative care team engagement</li> </ul>	<ul style="list-style-type: none"> <li>• Psychosocial support for parents, siblings, and other family members (grandparents)</li> <li>• Engagement with advocacy groups and other support services</li> <li>• Home nursing</li> <li>• Respite care</li> </ul>	<ul style="list-style-type: none"> <li>• Psychosocial support for parents, siblings, and other family members (grandparents)</li> <li>• Engagement with advocacy groups and other support services</li> <li>• Home nursing</li> <li>• Bereavement support</li> </ul>

**FIGURE 2.** Goals evolve as CLN2 disease progresses. PPR, photoparoxysmal response; IPS, intermittent photic stimulation; EEG, electroencephalography; WM, white matter; MRI, magnetic resonance imaging. (The color version of this figure is available in the online edition.)

	Early Stage	Rapidly Progressive Stage	Late Stage
<b>Major Clinical Findings</b>	<ul style="list-style-type: none"> <li>• Early language delay</li> <li>• Unprovoked new-onset seizures</li> <li>• Ataxia</li> </ul>	<ul style="list-style-type: none"> <li>• Seizures, often polymorphic and drug-resistant</li> <li>• Rapid decline of language ability</li> <li>• Rapid decline of motor function</li> <li>• Myoclonus</li> <li>• Sleep disturbance</li> <li>• Pain</li> <li>• Vision impairment</li> <li>• Behavioral symptoms (e.g., anxiety, agitation)</li> </ul>	<ul style="list-style-type: none"> <li>• Loss of voluntary movement</li> <li>• Loss of communication</li> <li>• Continued drug-resistant seizures</li> <li>• Myoclonus, dystonia, spasticity</li> <li>• Sleep disturbance</li> <li>• Blindness</li> <li>• Gastrostomy tube-dependent</li> <li>• Pain</li> <li>• Behavioral symptoms</li> <li>• Respiratory problems</li> </ul>
<b>Seizure Management</b>	<ul style="list-style-type: none"> <li>• Medication</li> </ul>	<ul style="list-style-type: none"> <li>• Medication</li> <li>• Ketogenic diet</li> </ul>	<ul style="list-style-type: none"> <li>• Medication</li> <li>• Ketogenic diet</li> </ul>
<b>Movement Disorder Management</b>		<ul style="list-style-type: none"> <li>• Medication</li> <li>• Physical therapy</li> <li>• Adaptive devices</li> </ul>	<ul style="list-style-type: none"> <li>• Medication</li> <li>• Physical therapy</li> <li>• Adaptive devices</li> </ul>
<b>Physical, Occupational, Speech/Feeding, and Complementary Therapies</b>	<ul style="list-style-type: none"> <li>• Speech therapy</li> <li>• Physical therapy exercises</li> </ul>	<ul style="list-style-type: none"> <li>• Exercises to maintain function and independence</li> <li>• Adaptive devices</li> <li>• Complementary therapies (e.g., music, hydrotherapy, hippotherapy) as adjunct strategies to manage symptoms and enhance quality of life</li> <li>• Augmentative and alternative communication</li> <li>• Feeding therapy</li> <li>• Environmental modifications for home and school</li> </ul>	<ul style="list-style-type: none"> <li>• Exercises to maintain range of motion</li> <li>• Adaptive devices</li> <li>• Complementary therapies as adjunct strategies to manage symptoms and enhance quality of life</li> <li>• Augmentative and alternative communication</li> <li>• Feeding therapy</li> <li>• Environmental modifications for home and school</li> </ul>
<b>Nutrition, Gastrointestinal, and Secretion Management</b>		<ul style="list-style-type: none"> <li>• Monitor nutritional status</li> <li>• Feeding and swallowing assessments</li> <li>• Pharmacologic and nonpharmacologic interventions to manage secretions</li> <li>• Monitor aspiration risk</li> <li>• Manage constipation</li> <li>• Manage gastroesophageal reflux</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor nutritional status</li> <li>• Feeding and swallowing assessments</li> <li>• Tube feeding</li> <li>• Pharmacologic and nonpharmacologic interventions to manage secretions</li> <li>• Monitor aspiration risk</li> <li>• Manage constipation</li> <li>• Manage gastroesophageal reflux</li> </ul>
<b>Respiratory Management</b>	<ul style="list-style-type: none"> <li>• Vaccinations</li> </ul>	<ul style="list-style-type: none"> <li>• Vaccinations</li> </ul>	<ul style="list-style-type: none"> <li>• Vaccinations</li> <li>• Pulmonary hygiene</li> <li>• Medication</li> <li>• Oxygen therapy</li> </ul>
<b>Management of Sleep Disturbance</b>		<ul style="list-style-type: none"> <li>• Sleep assessments</li> <li>• Nonpharmacologic strategies (e.g., establish regular bed time, music, massage)</li> <li>• Medication</li> </ul>	<ul style="list-style-type: none"> <li>• Sleep assessments</li> <li>• Nonpharmacologic strategies</li> <li>• Medication</li> </ul>
<b>Pain Management</b>		<ul style="list-style-type: none"> <li>• Pain assessments, including regular discussions with parents/caregivers</li> <li>• Medication</li> <li>• Nonpharmacologic strategies (e.g., complementary therapies, positioning aids, frequent repositioning)</li> </ul>	<ul style="list-style-type: none"> <li>• Pain assessments, including regular discussions with parents/caregivers</li> <li>• Medication</li> <li>• Nonpharmacologic strategies</li> </ul>
<b>Ophthalmologic Management</b>		<ul style="list-style-type: none"> <li>• Ophthalmologic examination</li> <li>• Avoid retina-toxic medications</li> </ul>	<ul style="list-style-type: none"> <li>• Ophthalmologic examination</li> <li>• Avoid retina-toxic medications</li> </ul>
<b>Social and Educational Interventions</b>		<ul style="list-style-type: none"> <li>• School and community participation</li> <li>• Augmentative and alternative communication</li> </ul>	<ul style="list-style-type: none"> <li>• School and community participation</li> <li>• Augmentative and alternative communication</li> </ul>
<b>Management of Behavioral Symptoms</b>		<ul style="list-style-type: none"> <li>• Environmental modifications to remove behavioral triggers</li> <li>• Psychology/psychiatry consultation</li> <li>• Medication</li> </ul>	<ul style="list-style-type: none"> <li>• Environmental modifications to remove behavioral triggers</li> <li>• Psychology/psychiatry consultation</li> <li>• Medication</li> </ul>
<b>General Pediatric Care</b>	<ul style="list-style-type: none"> <li>• Vaccinations</li> <li>• Dental care</li> </ul>	<ul style="list-style-type: none"> <li>• Vaccinations</li> <li>• Dental care</li> </ul>	<ul style="list-style-type: none"> <li>• Vaccinations</li> <li>• Dental care</li> </ul>
<b>Genetic Counseling</b>	<ul style="list-style-type: none"> <li>• Biochemical and molecular testing of proband</li> <li>• Genetic risk assessment in family and molecular testing</li> </ul>	<ul style="list-style-type: none"> <li>• Continue extended family genetic testing/counseling for those at risk</li> </ul>	
<b>Other</b>	<ul style="list-style-type: none"> <li>• Reassess medications</li> </ul>	<ul style="list-style-type: none"> <li>• Reassess medications</li> </ul>	<ul style="list-style-type: none"> <li>• Reassess medications</li> </ul>

**FIGURE 3.** Management strategies for CLN2 disease. (The color version of this figure is available in the online edition.)

four AEDs even in the later stages of disease should prompt a critical evaluation of necessity.

Although there are no formal contraindications, some AEDs have an adverse event profile in children with CLN2

disease; for example, carbamazepine and phenytoin should be used with caution as these may exacerbate myoclonus.<sup>31</sup> Some agents may exacerbate other symptoms of the disease (e.g., side effects of topiramate include speech impairment

**TABLE.**  
Common Medications Used by Experts to Treat CLN2 Disease Symptoms

Symptom	Medications
Seizures	Benzodiazepines (clobazam, clonazepam), ethosuximide, lamotrigine, levetiracetam, phenobarbital, valproic acid, zonisamide; most commonly used is valproate in various add-on combinations
Myoclonus	Benzodiazepines (clobazam, clonazepam), lamotrigine, levetiracetam, phenobarbital, valproate, zonisamide
Spasticity	Baclofen, benzodiazepines (diazepam), intramuscular botulinum toxin (focal), phenobarbital, tizanidine
Dystonia	Baclofen, benzodiazepines, clonidine, tizanidine, trihexyphenidyl
Secretions	Enteral atropine, intraglandular botulinum toxin, glycopyrrolate, inhaled ipratropium bromide, transdermal scopolamine (hyoscine)
Pain	Simple analgesia (acetaminophen, NSAIDs); stronger analgesics (methadone, morphine, hydromorphone); others (amitriptyline, clonidine, gabapentin, pregabalin)
Breathing difficulties	Albuterol
Mucus	Dornase alfa

Abbreviations:

NSAID = Nonsteroidal anti-inflammatory drug

Medications are listed alphabetically and do not represent an all-inclusive listing.

and psychomotor slowing). Medication regimes should be re-evaluated periodically, particularly when there is a new emerging symptom or a change in seizure pattern; the importance of reassessment is underscored by a report that describes two patients with CLN2 disease who developed status dystonicus after long-term valproate treatment that resolved only after the withdrawal of valproate.<sup>43</sup> For appropriate medication selection, it is important to distinguish epileptic seizures from nonepileptic events, including movement disorder (e.g., dystonia), pain, boredom, and fear.

The ketogenic diet may also have a role in the treatment of drug-resistant seizures in CLN2 disease and other NCLs.<sup>44</sup> Adherence to the diet can be challenging, although implementation is easier when a child is tube-fed. The burden of this diet has to be carefully balanced against the anticipated benefits. Any child on a ketogenic diet should be closely monitored for side effects and possible complications (e.g., constipation, kidney stones, growth retardation).

Emergency seizure management plans for home and school should be provided to the family and caregivers, with instruction on first aid, when to call an ambulance, and the risks versus benefits of rescue medication use at home (such as buccal or intranasal midazolam, rectal diazepam).<sup>45</sup>

### Management of movement disorders

Children with CLN2 disease typically present with different types of movement disorders. Myoclonus (epileptic and nonepileptic) is a hallmark feature of CLN2 disease.<sup>1,9</sup> Dystonia and spasticity are also common findings; chorea, athetosis, and tremors may also be seen. Status dystonicus and myoclonic status can be life-threatening

complications. Although rarely seen in the classic late-infantile phenotype of CLN2 disease, parkinsonism, prominent ataxia, and prominent chorea have been reported in atypical phenotypes.<sup>16,21–23</sup> Diagnosis requires clinical observation of the abnormal movements; obtaining video recordings is often very helpful. EEG with simultaneous electromyography may be used to distinguish myoclonic seizures from nonepileptic myoclonus but seldom leads to a change in management.

Because these neurological symptoms are generally difficult to control, the goals of medical management are to diminish their severity and frequency; maintain posture, range of motion, and function; prevent pain; and maintain quality of life. Pharmacologic treatment of the movement disorders common in CLN2 disease is shown in Table. AEDs are generally used to treat both epileptic and nonepileptic myoclonus, but, as noted previously, these should be selected with caution and re-evaluated periodically as certain agents may exacerbate other symptoms. Physical therapy and other interventions such as ankle-foot orthoses and adaptive equipment (gait trainers, therapy chair, lateral pillow, neck support and vests, etc.) are adjuvant strategies that may be considered to aid treatment of these symptoms.

### Physical, occupational, speech, and complementary therapy interventions

The ability of children with CLN2 disease to perform and participate in daily activities diminishes as motor, cognitive, and visual impairments progress. Physical and occupational therapies should be implemented early in the disease course to maintain function and independence for as long as possible and to prevent or delay complications (e.g., pain, joint contractures). These therapies should be tailored to the child's strengths, abilities, and motivation level, as well as to the family's goals. The recommended frequency of physical therapy sessions is two to three times per week, although this may depend on local resources and service configuration. Caregivers should be instructed on exercises, posture, and positioning so that these can be integrated into daily routines. Because children with CLN2 disease lose skills rapidly, early use of adaptive devices is recommended. Therapy chairs and standing and walking devices can support age-appropriate positioning/posture for daily activities (e.g., play, communication) and the functioning of muscles involved in eating and speaking, reduce the impact of spasticity and dystonia, and enhance breathing and digestion. Orthoses may be used to provide additional stability. It is important to anticipate the use of adaptive devices in the context of rapid disease progression as customization and reimbursement require time. Caregivers should be advised on home adaptations to accommodate physical disabilities and cognitive impairments (e.g., ramps, hoists). The Physiotherapy Evidence Database (PEDro)<sup>46</sup> may serve as a useful resource for physical therapists who are seeking evidence-based approaches for particular symptom concerns.

To reduce the severity of and complications due to the complex movement disorder symptoms, early initiation of physical therapy and use of medical aids, such as standing devices, orthoses, and bandages, is recommended. Physical therapy techniques to stretch the muscles and stabilize



pressure toward the joints can regulate muscle hypertonus (such as spasticity and myoclonus). Positioning, medical aids, and devices may also be implemented to help regulate excessive muscle tone. For myoclonus, positioning the child on the more heavily impaired side allows the child's body weight to exert a regulating effect on tonus, leading to reduction of hypertonic muscle activity. Through physical therapy intervention, improved posture and normotonic movement patterns can be supported.

Early referral to speech/orofacial myofunctional therapy is recommended for periodic evaluations of swallowing, feeding, and communication skills. Use of alternative and augmentative communication methods, such as symbols and gestures, may be helpful in managing speech/language impairment<sup>47</sup> and should be initiated early to enable children to maintain meaningful communication and social interactions after loss of speech. Because cognitive decline is progressive, children should be introduced to alternative and augmentative strategies as early as possible while new learning can still take place.

Although much research is still needed to establish a clear evidence base for CLN2 disease and other pediatric neurodegenerative disorders, certain complementary therapies have been used to good effect in a range of pediatric neurodevelopmental conditions.<sup>48–50</sup> Complementary therapies, such as hippotherapy, hydrotherapy, and music therapy, may be considered for children with CLN2 disease to decrease anxiety, pain, and boredom and to provide opportunities for social interaction and enjoyment. As hearing is preserved, music is often a source of comfort to these children, especially as other skills are lost.

### **Nutritional, gastrointestinal, and secretion management**

As CLN2 disease progresses, swallowing difficulties will arise and worsen until oral feeding fails to meet nutritional requirements and/or the risk of aspiration is high. Cardio-respiratory failure and sepsis secondary to aspiration pneumonia are common causes of death in these children, hence managing secretions is critical. Pharmacologic (Table) and nonpharmacologic interventions (e.g., suctioning, oral care, physiotherapy, corn silk tea<sup>51</sup>) to manage secretions are recommended. Parents/caregivers should be taught to recognize and alert clinicians to early signs of dysfunction, such as coughing, choking, and respiratory distress during meals. As problems with dysphagia increase, the management of oral secretions/saliva becomes more complex. Drooling from the mouth or pooling of secretions at the back of the throat has a major impact on the quality of life of the child and family. A stepwise program of anticholinergic treatment is necessary, starting with inhaled ipratropium bromide, transdermal hyoscine, or enteral glycopyrrolate; side effects such as urinary retention and constipation may be observed, together with less obvious problems of blurred vision, irritability, and headache, particularly as doses increase.<sup>52–54</sup> Regular intermittent low-dose botulinum toxin injections to the saliva glands may be necessary to control symptoms and minimize systemic side effects.<sup>52,55,56</sup>

Feeding difficulties can be very distressing and disruptive for families and can lead to nutritional deficiencies. Nutritional management is a critical component of patient care and includes maintaining adequate energy and fluid

intake. Fortified foods and dietary supplements may be required to meet nutritional needs, although high-calorie fortified foods may not be well tolerated and may lead to diarrhea. While the child feeds orally, swallowing should be assessed frequently and the potential for aspiration should be monitored. Caregivers should be educated on appropriate food and fluid consistencies, the most suitable positioning, and monitoring. Ideally, a multidisciplinary feeding and nutrition team that includes a dietitian, gastroenterologist, speech/feeding therapist, physical/occupational therapist, nurse, and psychologist should work with the child and family to address feeding concerns.

Tube feeding (nasogastric or gastric tube) is recommended when the risk of aspiration is high, when the child can no longer swallow or struggles to eat (dysphagia), when weight loss/nutritional deficiencies are observed, or when the family struggles to feed the child. Children who are gastrostomy tube dependent should also be monitored frequently, and advice on gastrostomy tube home care and enteral feeding should be available to caregivers. Severe gastroesophageal reflux may increase the risk of aspiration. Proton-pump inhibitors are often used for gastroesophageal reflux disease,<sup>57</sup> but fundoplication may need to be considered if other approaches have failed. Of note, parents often struggle with the decision for tube placement; for some, gastrostomy tube feeding signifies the end stage of disease, and loss of the nurturing experience of feeding may also have a profound psychological impact on caregivers. Early engagement with a palliative care team to discuss milestone losses and to set expectations is beneficial.

Constipation is a common complication in CLN2 disease, which, if left untreated, can cause pain and exacerbate both seizures and movement disorder. Preventive measures to manage constipation include ensuring sufficient intake of liquids, dietary changes to increase fiber intake, stool softeners, dysmotility agents, and/or laxatives.

### **Respiratory management**

Respiratory problems in the late stage of CLN2 disease can be life threatening. Interventions include vaccinations for children and family members against preventable respiratory diseases (e.g., pneumococcal and influenza vaccines), regular pulmonary hygiene (e.g., using mucolytics, high-frequency chest wall oscillation, mechanical insufflator-exsufflator devices), and bronchodilators (Table). Supplemental oxygen is not routinely used but may be provided in some cases.

### **Management of sleep disturbance**

Sleep disturbance is common in CLN2 disease; one study revealed that 93.8% of patients with CLN2 disease (n = 16) had sleep difficulties.<sup>15</sup> Poor sleep quality can greatly impair the quality of life of affected children and their families. Sleep disturbances may include difficulties in falling asleep and staying asleep, waking due to myoclonus, daytime sleepiness, and sleep-disordered breathing.<sup>15</sup> Moreover, poor sleep can adversely affect seizure control and exacerbate behavioral and cognitive impairments. Polysomnography may influence the management of children who snore.<sup>15</sup> Intervention will depend on the stage of

disease and consideration of the risks and benefits to the child. Behavioral strategies<sup>58</sup> (e.g., good sleep hygiene), environmental strategies<sup>58</sup> (e.g., music, massage, weighted blankets), and medications (e.g., melatonin, chloral hydrate, clonidine, pregabalin) may be helpful in treating sleep dysfunction.

### Ophthalmologic considerations

Visual dysfunction in CLN2 disease results from both retinal and central nervous system (CNS) pathway degeneration. As with other CNS structures, the secondary visual pathway projections within the brain appear to progressively degenerate with disease progression. At the level of the eyes, CLN2 disease appears to primarily affect the retina, in a manner similar to that seen in chloroquine/hydroxychloroquine toxicity. A gradually progressive retinal degeneration, commencing at the level of the outer retina and progressing from the central macula to the periphery, is a characteristic manifestation of CLN2 disease.<sup>59</sup> The severity of the ophthalmologic findings has been shown to correlate with worsening neurological function and advancing age.<sup>59</sup> Ultimately, this retinal degeneration results in widespread retinal atrophy and leads, in combination with the CNS visual pathway deterioration, to vision loss. Affected children are typically blind by age seven to ten years. No interventions are currently available to treat these ophthalmologic manifestations. Optical coherence tomography appears to be the most sensitive tool to detect the outer retinal changes and to establish the extent of retinal degeneration. Use of retina-toxic medications (or any other agents that have direct toxicity to the retina) should be avoided (e.g., hydroxychloroquine, thioridazine, vigabatrin). There is no evidence to suggest that polarized sunglasses or antioxidants are effective in mitigating the retinal degeneration.

### Management of pain and distress

Pain in children with CLN2 disease can originate from multiple sources, including musculoskeletal (e.g., spasticity, dystonia), gastrointestinal (constipation, reflux, dysmotility), urinary retention, corneal abrasions, and skin breakdown. Effective treatment requires determination of the source(s) of pain if possible, which can be particularly challenging when the child has lost verbal communication. It is also important to distinguish pain from other causes of discomfort; for example, fear, anxiety, loneliness, or boredom may manifest as grunting and be misinterpreted as pain.

The language, motor, cognitive, and visual impairments of affected children limit the ability to assess pain. In the absence of a standardized tool for evaluating pain in CLN2 disease, it is essential to address pain regularly in discussions with caregivers and to value their perceptions, particularly when the child cannot communicate verbally. Some tools used to assess pain in children with communication difficulties, such as the Pediatric Pain Profile<sup>60</sup> or the Non-Communicating Children's Pain Checklist,<sup>61</sup> may be helpful but have not been directly validated for patients with CLN2 disease. A preliminary study suggests that the Batten's Observational Pain Scale may be a useful tool for parents monitoring their child's pain in the home setting.<sup>62</sup>

Pain control and relief may be accomplished with medication (Table) and by nonpharmacologic interventions (e.g., complementary therapies, positioning aids, weighted blankets, physiotherapy, heat).

### Social and educational strategies and interventions

Social isolation is commonly experienced by children with CLN2 disease and their families. Providing support to maintain community integration is essential. Although affected children are typically unable to walk or talk and are visually impaired by age six years, hearing is preserved and they have the capacity to connect meaningfully with people. As previously noted, augmentative and alternative communication strategies can be beneficial and should be introduced while the child can still learn to use these approaches. Maintaining school attendance as long as possible is desirable to allow children to be engaged with peers and to benefit from educational and sensory experiences in the classroom. School also coincidentally provides much needed respite for caregivers. Families should work closely with the health care team and school staff to ensure that their child's needs are met in the school setting, including reasonable adaptations to accommodate physical, cognitive, and behavioral impairments and emergency management of seizures. In developing an individual educational plan, families and school personnel should consider the various adverse educational impacts of CLN2 disease and consider how to create a school experience that can mitigate these impacts. Importantly, school personnel may need to undergo a paradigm shift in approach, from the traditional educational model of successive achievements that build over time to a model that is focused instead on the maintenance of functional abilities (for as long as possible) and then adaptation to loss of function as the disease progresses further.

### Management of behavioral symptoms

Children with CLN2 disease often exhibit behavioral symptoms, although these have not been well characterized. Anxiety and agitation are common problems that can cause great suffering to these children and distress to caregivers. Nonpharmacologic intervention should include prevention by identifying and modifying triggers (situations, settings, people) that lead to negative behaviors. Pain and sleep disturbance may be precipitating factors in these children, as well as possible consequences of behavioral problems. Behavior management strategies should evolve over time as the disease progresses, with growing emphasis on modifying the environment and expectations rather than on training the child. Referrals to a child psychologist or consultation with a psychiatrist for medication advice may be considered as part of the management strategy. Neuroleptic drugs should be avoided if possible because there is a risk of extrapyramidal symptoms as side effects from these medications.<sup>63</sup>

### End-of-life care considerations

Prevention of pain should be a major goal at the end of life. Opioids and sedatives may be necessary to achieve



adequate pain control. Measures to ensure respiratory comfort include oxygen therapy, anticholinergics, opioids, and sedatives. Frequent repositioning, positioning aids, and barrier creams are effective for prevention of skin irritation. Reduced gut absorption may be seen in the final stage of disease and should be discussed with families as part of end-of-life care planning.

Hospice care and home palliative care services should be offered to all patients with CLN2 disease, although it is recognized that access to such care varies within and between countries and major barriers to care provision may exist. Psychosocial support for the family is essential throughout the course of the disease but becomes especially critical at the end of life. It is important for clinicians to listen to families, encourage advanced end-of-life care planning and decision making, and respect the wishes of families, including “do not resuscitate” orders and non-escalation of care.

### Other considerations

Children with CLN2 disease typically take multiple medications daily (commonly 10–12) and additional medications as needed for acute symptom exacerbations, therefore it is important to be mindful of potential drug-drug interactions. All medications, including long-standing prescriptions, should be regularly re-evaluated. Children should continue to receive general pediatric care (e.g., vaccinations, dental care). Cardiology assessments should be considered, as some patients may exhibit cardiac rhythm abnormalities.<sup>64</sup> Children receiving general anesthesia must be carefully monitored, as they may be at risk for perioperative complications such as hypothermia.<sup>65,66</sup>

### Family support

CLN2 disease profoundly affects the family unit. Family members living with and caring for an affected child typically experience significant psychological stress, social challenges, and financial strain<sup>67</sup> (Batten Disease Support and Research Association, unpublished family needs survey results) and will require support from health care providers and from the community. The physical well-being of family members may also be compromised from caring for an affected child<sup>67</sup>; for example, some caregivers report back and shoulder pain from injuries acquired from lifting and carrying their child and necessary equipment for daily activities. Family members also report sleep problems stemming from the need to be constantly alert for seizure activity and other signs of distress in their child.

Recognizing and monitoring the impact of the disease on caregivers and siblings, identifying appropriate interventions and services, and communicating and listening to family members with sensitivity and compassion are critical components of comprehensive care. Patient advocacy groups provide a forum for peer-to-peer support and can facilitate the provision of services and financial aid/grants; two of the largest and most established groups are the Batten Disease Family Association and the Batten Disease Support and Research Association, but other groups exist within different countries. At the time the news of the

diagnosis of CLN2 disease is delivered, families should be provided with information about the condition and relevant resources, as well as given the opportunity to ask questions and express concerns. Clinicians should be well prepared for this difficult encounter and be sensitive to the fact that this news often follows a protracted diagnostic odyssey of two or more years. Helpful information regarding communicating difficult news to parents is available (e.g., from the Royal College of Nursing<sup>68</sup>). Palliative care team engagement should be initiated early in the disease course. It is important to support families to plan in advance for the rapid and relentless disease progression. Genetic counseling/family planning should be offered to family members and the genetic risk assessed for siblings, subsequent pregnancies, and first-degree relatives as appropriate. Ongoing feelings of grief and loss should be anticipated, and memory-making activities encouraged. The needs and skills of caregivers should be regularly assessed to ensure effective home care of these children.<sup>69</sup> Home nursing care, social services, and bereavement support are of value at the end of life and beyond.

### Future perspectives

Disease-modifying therapies are being developed,<sup>1,31,70</sup> and clinical trials for enzyme replacement therapy<sup>27,71</sup> and gene therapy<sup>72,73</sup> are currently underway. Greater disease awareness and earlier diagnosis will facilitate timely initiation of CLN2-specific management strategies and future disease-modifying therapies, which have the potential to improve outcomes.

Existing strategies and best practice guidelines for children with complex neurodisability currently inform the management of children diagnosed with CLN2 disease. In pediatric-onset dementias, the refinement of these existing strategies may be necessary to further optimize care for affected children and their families. As gaps in knowledge remain and current practice varies among settings, the opportunities to explore therapeutic differences and options by means of observational studies, clinical registries, and clinical trials should not be missed. Importantly, improved tools for the standardized assessment of CLN2 disease symptoms, including cognition, mood/behavior, sleep, and pain, are needed. Further characterization of the phenotypic spectrum will facilitate early diagnosis and optimal outcomes.

The management practices presented here reflect a broad consensus among this group of experts; as new research and therapies become available, it will be imperative to establish and then regularly revise consensus-based management guidelines for this disease.

### Conclusions

CLN2 disease is a pediatric-onset neurodegenerative condition with a complex array of symptoms. A multidisciplinary approach to management is essential for optimal care and quality of life of patients and families. Effective strategies currently exist to manage many of the symptoms of CLN2 disease. Disease management practices around the world are generally consistent among experts and are drawn from experience gained from other conditions.

Although gaps in knowledge remain, this effort to identify common management practices represents a significant step toward the development of consensus-based management guidelines.

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