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Clinical Practice Guideline for Adolescent and Adult Patients with Spinal Muscular Atrophy – Part 2

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Abstract: In recent years, the field of spinal muscular atrophy (SMA) has made progress in multidisciplinary care and disease-modifying therapies (DMTs). Survival and the quality of life of patients have significantly improved. However, no clinical practice guidelines exist for the management of SMA in adult and adolescent patients. Multidisciplinary experts from a number of tertiary medical centers in China, specializing in the diagnosis and treatment of SMA, came together to remedy this using evidence-based medicine. This guideline serves as an instrumental reference for the standardized care of Chinese SMA patients.

Keywords: Spinal Muscular Atrophy; Diagnosis; Multidisciplinary Treatment; Disease Modifying Therapy.

6.4. Rehabilitation management

6.4.1. Functional assessment

In the management of patients with SMA, rehabilitation plays an important role. While young children with SMA have different needs than adolescent and adult SMA patients, whereas the latter have higher demands for independent living and greater requirements for limb function and activities of daily living. In rehabilitation management, it is important to regularly assess the patient's status to formulate and adjust rehabilitation plans at different stages. The results of functional assessment are an important criterion for measuring the efficacy of drug treatment. [1,2] Under the theoretical framework of the International Classification of Functioning, Disability, and Health (ICF), the assessment should comprehensively observe the patient's multi-dimensional performance. This includes motor function, joint range of motion, contractures, muscle weakness, posture control, scoliosis and pelvic obliquity, hip dislocation, sitting tolerance, chest deformities, fatigue, activities of daily living, social ability and family care. [3-7]

This section on functional assessment introduces ten assessment tools suitable for patients with SMA in sections 6.4.1 to 6.6.10. The assessment standards include gross motor function, operational capacity, activities of daily living, and swallowing function. In 6.4.1.11, there are combination suggestions given for various patient types that can be referenced for clinical application.

6.4.1.1. Hammersmith Functional Motor Scale Expand (HFMSE)

HFMSE is a tool mainly used to evaluate gross motor function in patients with SMA. The original scale, the Hammersmith Functional

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Motor Scale (HFMS), was specifically created for SMA patients by British physical therapists. [8] The HFMSE was further improved by American researchers. [9] The expanded version includes 13 additional items adapted from the Gross Motor Function Measure (GMFM), which are closely related to motor function in patients with SMA type 2 and type 3. After completing the validation study, the HFMSE has become widely used in SMA natural history research and new drug clinical trials. It is now one of the most commonly used motor function assessment scales in the SMA field. [10,11]

Recommendation: HFMSE is widely used for functional assessment of SMA patients, with mature validation studies and natural history data (Class I recommendation, Level B evidence).

6.4.1.2. Revised Upper Limb Module for SMA (RULM)

RULM is mainly used to assess the upper limb function of SMA patients. Its items include the evaluation of specific upper limb functions under particular conditions. The results provide a comprehensive reflection of the ability of the affected upper limbs, including muscle strength, contractures, posture restrictions, growth and development. The original Upper Limb Module for SMA (ULM) was developed by clinicians, physical therapists, researchers, and patient advocacy groups to assess the upper limb function of ambulatory SMA patients, mainly children. [12] ULM has been widely used in SMA natural history studies [13,14] and ongoing clinical trials after being validated in multicenter settings. To make it applicable to a broader SMA population, the scale was revised and expanded to form the current RULM, which is suitable for individuals aged 30 months to adulthood. [15]

Recommendation: RULM has been used as a tool to evaluate upper limb function in patients with SMA in many studies with a high sample size (Class I recommendation, Level B evidence).

6.4.1.3. Children's Hospital of Philadelphia Adult Test of Neuromuscular disorders (CHOP-ATEND)

CHOP-ATEND is a revised version of the CHOP-INTEND. This new scale has been modified to exclude items 11, 15, and 16, which are not suitable for adult testing, making it more appropriate for the assessment of adults. [16] There are 14 assessment items in total, completed in two postures, including six items in the semi-recline position and eight items in the upright sitting position, with a total score of 46 points. The scale evaluates critical movement abilities of the neck, trunk, arms, and hands. It is primarily designed for patients who can only sit or cannot sit alone due to neuromuscular disorders. This scale is more sensitive to patients whose movement ability is significantly reduced, avoiding the floor effect in the upper limb GMFM.

CHOP-ATEND was collaboratively developed and modified by a group of international physical and occupational therapists. The relevant website of Stanford University (https://med.stanford.edu/daylab/atend.html) offers assessment scales, manuals, and study materials related to this tool. Physicians can also communicate, consult, or provide feedback to members of the working group online.

Recommendation: CHOP-ATEND is more friendly to patients with weak muscle strength and poor function, and is more suitable for patients with SMA who cannot sit alone or for long periods (Class II recommendation, Level C evidence).

6.4.1.4. Motor function measure (MFM-32)

MFM-32 is a comprehensive method of evaluating motor function that can help monitor the functional status and progression of most patients with neuromuscular diseases. The process of developing and validating MFM-32 began in 1998. Experts in physical medicine, neurology, and pediatrics in Europe and North America analyzed and tested seventy-five assessment components to create the first edition of the assessment scale, which contained 51 items. After a validation study from May 2000 to February 2001, the second edition of the assessment scale was created, which contained thirty-two items and was called MFM-32. MFM-32 has proven to be highly effective in evaluating 303 patients aged 6-60 years with typical neuromuscular diseases, including 35 patients with SMA. [17] In a study evaluating patients with SMA types 2 and 3, MFM-32 has high responsiveness and sensitivity, which helps monitor changes in exercise capacity during the disease progression in patients with types 2 and 3. [18]

Recommendation: Patients' motor function can be comprehensively assessed and evaluated through MFM-32, which also offers a channel for online communication to maintain consistent results. (Class II recommendation, Level C evidence).

6.4.1.5. Timed Up and Go test (TUGT)

TUGT is a quick method to assess walking ability. It was initially used to evaluate the balance, walking ability, and fall risk of older people. It has the advantage of being easy to master, convenient to apply, and accurate in quantification, making it suitable for clinical evaluation and research. This test was first developed by Podisadle and Richardson based on Mathias's "Get-up and go" test. [19,20] According to the results of a questionnaire survey of neurologists, rehabilitation doctors, and rehabilitation therapists in 10 clinics in Canada, the test-retest reliability of TUGT assessment is high among ambulatory patients with SMA. [21] At the same time, TUGT significantly correlates with lower limb muscle strength, HFMSE score, 10-meter walk/run, and 6-Minute Walk Test (6MWT) distance. [22]

Recommendation: TUGT can be used as a follow-up test for ambulatory patients to observe their balance and walking stability (Class IV recommendation, Level D evidence).

6.4.1.6. 6-Minute Walk Test

Field walking test is often used to evaluate exercise capacity and access prognosis, especially the treatment response of chronic respiratory diseases. [23] The 6MWT is highly effective in all field walking tests. It's easy to conduct, well-tolerated, and more reflective of activities of daily living than other walking tests. [24] This test evaluates the overall response of related systems during exercise, such as the cardiovascular, neuromuscular units, and muscle metabolism. In 2002, the American Thoracic Society (ATS) issued guidelines for 6MWT, [25] and in 2014, the European Respiratory Society and ATS updated the systematic review [26] and technical standards [23].

Recommendation: 6MWT can be used to assess accessing walking ability. To ensure the quality of assessment, factors such as venue, test time, tester's password and patient's physical ability should be strictly controlled (Class II recommendation, Level C evidence).

6.4.1.7. Range of motion (ROM)

ROM is an essential tool used by rehabilitation therapists to evaluate the limb status of SMA patients. Joint contracture is common in SMA patients, which can involve areas such as the shoulders, elbows, wrists, fingers, hips, knees, ankles, and toes. Even in limbs without muscle weakness, joint contracture significantly affects patients' motor function and causes functional hindrance. A study in Taiwan, China has shown that the joint range of motion limitations is positively correlated with age and upper-extremity functional grade among patients with type 2 SMA($P<0.001$). [27] Another study has shown that in patients who have maintained sitting for a long time and want to stand with the help of a standing bed or a walker, hip and knee joint mobility directly affects the quality of assisted standing training. [28] There are similar reports in terms of upper limb mobility. [29] Therefore, ROM should be added to the SMA assessment to help rehabilitation therapists formulate and adjust prescriptions regarding daily treatment programs, stretching, orthotics use, and standing training for patients with different SMA types promptly.

Recommendation: ROM shows the patient's joint contracture status and serves to observe changes and warn of contractures (Class II recommendation, Level C evidence).

6.4.1.8. Spinal Muscular Atrophy Functional Rating Scale (SMAFRS)

SMAFRS is a revised version based on the modified Amyotrophic Lateral Sclerosis Functional Rating Scale and the Functional Independence Measure for Children. This scale contains various subsets that are scored by the patient or caregiver based on their level of independence, ranging from 0 (completely dependent) to 5 (completely independent). The maximum score that can be achieved is 50. [30] The SMAFRS primarily focuses on activities of daily living that require the use of upper limbs, such as feeding, dressing (upper and lower body), bathing, toileting, position adjustment in bed, transferring, walking, and climbing stairs.

When assessing the effects of drug treatment on SMA patients, SMAFRS is used along with HFMSE and RULM. [31] Even if a patient has severe physical disability and cannot be assessed using HFMSE and RULM, SMAFRS can still be employed. SMAFRS is based on the subjective evaluation of the patient or caregiver and better reflects the patient's difficulty in completing the same target action. Patients and caregivers, although not trained professionals, are witnesses of life and have more in-depth observations of patients' functional

performance. In addition, professionals can also use this scale to make accurate assessments of patients' functional status.

Recommendation: SMAFRS can provide a targeted assessment of the degree of dependence of patients with SMA (Class II recommendation, Level C evidence).

6.4.1.9. 36-Item Short Form Survey (SF-36)

SF-36 is used to assess the quality of life. It evaluates eight dimensions of health-related quality of life (HRQoL), including physical functioning (PF), role-physical (RP), bodily pain (BP), social functioning (SF), mental health (MH), role-emotional (RE), role-emotional (VT), and general health (GH). [32] As SMA patients age, they take on more social roles, and changes in their physical abilities can affect their quality of life and social interactions. In turn, mental state also affects physical function. Many patients with mild SMA have low mental component scores, and psychological intervention can reduce the impact of emotional distress on physical functions which helps improve rehabilitation. [33] In addition, the optimization of SF-36 in the social dimension can bring the advantages of increased information exchange and more participating caregivers, forming a more diversified system for the patient's care structure. Therefore, it can play a good role in SMA rehabilitation management. [34]

Recommendation: SF-36 has a broader scope than other scales and is very helpful in describing patients' living abilities and their living status (Class II recommendation, Level C evidence).

6.4.1.10. Swallowing function assessment

The evaluation of swallowing dysfunction typically involves two types of assessments: bedside assessment and instrumental assessment. Professionals and speech therapists utilize a combination of medical history, facial and oral examination, and swallowing study to determine the degree of a patient's swallowing disorder. However, there is currently no universally accepted screening tool for assessing swallowing dysfunction in SMA patients. Generally, ambulatory patients do not have difficulty with swallowing, while non-ambulatory patients require more attention to ensure safe swallowing. These patients are often susceptible to aspiration and pulmonary infections. Barium swallow is recommended to be performed as soon as possible following a diagnosis. And any early signs should be closely monitored during subsequent follow-up visits. [3] This guideline has a dedicated section that offers detailed recommendations on the digestive and nutritional functions of SMA patients. It's important to combine both the digestive and nutritional parts of this article to provide a comprehensive assessment of the patient's swallowing disorder.

Recommendation: Swallowing disorders and aspiration should be taken seriously, and the swallowing assessment suitable for SMA patients needs to be further studied and verified (Class III recommendation, Level D evidence).

6.4.1.11. Holistic assessment package

Considering the advantages of many assessment tools mentioned above, many international experts believe that establishing a standardized functional assessment package will help improve understanding of disease development and treatment response. [4, 35-36]The heterogeneity and multi-system nature of the SMA disease determine that a diverse assessment scale system should be considered for different symptoms or stages of patients. Table 1 shows the application of the combination of the rehabilitation above assessment scale in SMA patients, including reports provided by patients and their families, objective assessment of gross and fine functions, quality of life surveys. CHOP-ATEND is based on CHOP-INTEND for children, but it doesn't consider the impact of contracture on scoring. However, for adults, joint contractures can have a significant effect on assessment results and training programs, so joint range of motion measurement is included in the assessment package for patients with severely reduced motion.

Recommendation: A combination of multiple scales should be considered for comprehensive assessment of patients with different types of SMA (Class II recommendation, Level C evidence).

6.4.2. Rehabilitation management strategies

This section aims to offer a general analysis and suggestions for the issues commonly faced by SMA patients. It serves as a clinical reference for healthcare professionals. Specific training recommendations, such as stretching time, active training amount, and brace wearing, should be customized based on the patient's specific needs and circumstances by

Target group	Activities of daily living	Functional status	Quality of life
Non-sitters	RULM CHOP-ATEND ROM	SMAFRS	SF-36
Sitters (can't stand)	RULM HFMSE MFM-32 ROM	SMAFRS	SF-36
Sitters (can stand with assistance)	RULM HFMSE MFM-32	SMAFRS	SF-36
Walkers	HFMSE MFM-32	SMAFRS TUGT 6MWT	SF-36

Table 1. Recommendations for motor function assessment of SMA patients with different functional status. RULM: revised upper limb module for SMA; CHOP-ATEND: Children's Hospital of Philadelphia Adult Test of Neuromuscular disorders; ROM: Range of motion; SMAFRS: Spinal muscular atrophy functional rating scale; SF-36: 36-Item Short Form Survey; HFMSE: Hammersmith Functional Motor Scale Expand; MFM-32: Motor function measure; TUGT: Timed up and go test; 6MWT: 6-Minute Walk Test.

rehabilitation physicians and therapists. The development of scientific rehabilitation programs usually requires repeated evaluations and adjustments to ensure its effectiveness and appropriateness

6.4.2.1. Rehabilitation management for SMA patients under the ICF framework

Maintaining physical function and mobility is a primary goal of SMA rehabilitation management, which plays a crucial role in improving patients' quality of life. The ICF concept of functional ontology highlights three aspects of human beings, which are body function and structure, activities, and participation. [6,37] Body functions and structures refer to the physiological abilities and the anatomical parts of the human body. Physiological abilities include the movement system that enables people to exercise. Structures, such as bones and good ligament extension, can support the human body and increase joint range of motion. The two aspects of activities and participation involve the patient as an individual who interacts with family and society, engages in external communication, self-care, work and study, family life, interpersonal communication, and other areas of life, all of which are increasingly impacted by rehabilitation therapists and doctors.

This guideline for rehabilitation management focuses on SMA non-sitters, sitters, and walkers. The focus is on body function and structure, taking into account the patient's activities and participation. Patients with SMA are classified based on their functional status, which includes non-sitters, sitters, and walkers (particularly adult patients).

Recommendation: The classification of patients according to function and structure is derived from the functional characteristics of various patients in the international classification of SMA. However, the definitions and boundaries of each type still need to be completed and verified in practice in the future.

6.4.2.2. Rehabilitation management of non-sitters

Non-sitters are the patients most severely affected by the disease. Patients cannot maintain a sitting posture independently due to deformation and weakness of the trunk and limbs or have never been able to sit independently during their growth. Non-sitters generally include type 1, 2, and older type 3 SMA patients. They usually exhibit severe muscle weakness throughout the body, significantly weakened proximal flexor muscles, reduced muscle tone, and only retain the active function of the distal part of the limbs. The mobility of their limbs is limited, with severely scoliotic spine and limited lying posture. In rehabilitation management, the primary goals should be to maintain and expand residual functions and minimize disease and secondary damage.

(1) Body positioning and posture control.
Non-sitters, due to scoliosis and joint contracture, spend long periods lying down or require auxiliary support when sitting. They are unable to adjust the position of their limbs or shift their center of gravity. When lying down, it is important to use supportive items, such as foam pads, quilts, rolls, or bean bags, to keep the patient in the supine or lateral position. The texture of the support should be moderately hard. If the support is too hard, it can compress the skin, and if it's too soft, it won't provide adequate support. When sitting, it's crucial to support the patient's head and neck, armpits, and side of the scoliosis to resist gravity. A padded support frame in a wheelchair or daily seat or restraint can keep the head, neck, or torso upright while sitting.

(2) Joint stretching and range of motion maintenance.
Non-sitters joint stretching and passive activities can begin when the patient's active movement decreases. Preventive manual stretching is still necessary even if the patient's limb movement has not yet been limited. Rehabilitation therapists should develop stretching methods based on joint location, restriction degree, and the functional status of the patient. Family members and caregivers should perform daily stretching activities for patients under rehabilitation therapists' regular supervision and guidance.
The stretching method relieves contracture, while passive movement maintains the range of motion. The purpose is to reduce the restrictions on body position and posture caused by joint contractures and improve the patient's comfort. The recommended minimum frequency for manual stretching and passive activities is five times per week, with daily sessions for better results.
Braces and orthotics can also stretch and correct joints such as orthotics for knee, ankle, foot, and hand splints. The single wearing time of the brace and orthosis should be more than 60 minutes, and the frequency of use should be maintained at least five times per week. [38] The brace can be worn for an extended period and even while sleeping, as long as the patient's body allows. It is important to regularly change the patient's position to prevent limb compression and twisting caused by the brace's weight and restraint pressure.

(3) Active movement ability and daily function.
During an assessment, it is crucial to identify and document as many of the patient's active movements as possible. These movements may include flexing and extending fingers, elbow flexion and extension, turning the head, and so on. These movements are essential for the patient to carry out daily independent activities, such as operating computers or mobile phones, sorting clothes, and grasping small objects. Based on the patient's functional movements and tolerance, the therapist can create a tailored training program that includes both independent movements and active assisted movements.
For non-sitters, assisted living equipment is crucial to maintain their daily independence. Some examples of such equipment include electric sleep to stand beds, adjustable electric wheelchairs, upper limb support platforms, limb suspension tools, bathtub position fixation devices, eye-tracking devices, and mouth-operated mouse. In today's society, personal computers and mobile phones have become essential tools for everyday life. They are user-friendly and have a significant impact, making them suitable for people with severe disabilities, such as SMA patients. These tools can significantly improve the patients' social participation and communication abilities.
Patients frequently experience issues such as bending of the trunk towards the dominant side of the upper limb, significant muscle weakness and more severe joint contracture on the non-dominant side. Therefore, it is important to pay attention to change their body position and center of gravity when providing care. It is recommended to move objects such as mobile phones and food to different locations, allowing patients to establish functional positions on different centers of gravity even if they can only use the dominant side of the limb.

Recommendation: Non-sitters have a high degree of disability and require extensive daily rehabilitation, including passive movement, positioning, and residual function maintenance. It is recommended that daily life be completed with the help of a dedicated carer and appropriate assistive life equipment (Level II recommendation, Level C evidence).

6.4.2.3. Rehabilitation management of sitters

Sitters typically include type 2 and 3 SMA patients, some of whom can stand with assistance but cannot walk. Compared to non-sitters, sitters have stronger limbs and less scoliosis, as well as sitting ability. Nonetheless, these patients often have significantly reduced upper limb muscle strength, and their proximal muscle groups are weaker than their distal muscle groups. While they can make slight lower limb movements, it is less helpful for them to maintain posture or change positions. Contracture and deformation of multiple joints in the body and scoliosis are also noticeable, but they are better than non-sitters. The primary goals of rehabilitation management for sitters are to prevent the progression of joint contractures and scoliosis, consolidate existing abilities, and strive for functional improvement.

(1) Body positioning and posture control.
Sitters have a greater capacity to control their position changes and posture. However, joint contracture and scoliosis still limit their position maintenance and active movement. Thoracolumbar orthotics is recommended to correct a patient's sitting posture while supporting posture maintenance. For those with sufficient trunk and upper limb strength, lateral support pads may suffice for maintaining a sitting position, though care should be taken to avoid hindering upper limb activities. When transitioning between positions, it is important to protect the head from potential neck injuries. If necessary, a neck brace can be worn to provide additional support.
Patients who can stand with assistance should be encouraged to practice standing using a standing frame, standing bed, or knee ankle foot orthosis. This practice is crucial as it helps to stretch the lower limbs while also strengthening the bones. Furthermore, maintaining an upright position at regular intervals can also promote the patient's social participation function.
(2) Joint stretching and range of motion maintenance.
The joint stretching of sitters is similar to that of non-sitters. Rehabilitation therapists should assess the patient's situation and formulate methods and plans. Family members and caregivers should do daily stretching for the patient under the guidance and regular supervision of professionals.
Sitters have a wider range of limb movement than non-sitters, but their muscle strength is still weaker. When doing large-scale stretching activities, the distal joints should be as relaxed as possible to avoid tears or fractures caused by rough movements and abnormal movement directions. The recommended minimum frequency for manual stretching is five times weekly, with daily sessions for better results.

Orthosis can still be used on the upper and lower limbs to improve the patient's mobility. The orthosis should be worn for at least 60 minutes, even during sleep, while monitoring skin pressure and sleep quality. The brace should be worn at least five times weekly. In patients who can stand with assistance, standing training can stretch the Achilles tendon. The duration of standing training should reach 30 to 40 minutes per time. Patients with insufficient lower limb endurance can use ankle or knee braces for auxiliary support, with the training frequency being 3 to 5 times per week. [38]
(3) Active movement ability and daily function.
Strength training should be included in the patient's daily routine. This training can improve strength, endurance, and balance, leading to better social participation and occupational ability. [39] Sitting and standing endurance training can increase the amount of time a patient is upright throughout the day, improving their ability to participate in social, learning, or occupational activities. Sitting training helps patients maintain a static sitting position or actively shift their center of gravity. Lower limb braces and a suspension frame can be used to increase standing time. Patients can also perform water-based assisted standing exercises.
Strength training of the neck, trunk and proximal joints is necessary. Muscle strength training can be carried out through active movements with the assistance of others. Daily movements such as turning over, sitting up, and transferring can also be used to train key muscle groups. The same attention should be paid to the coordinated development of bilateral muscle strength.

Recommendation: Sitters should maintain and enhance their ability to live independently in a sitting position (Class II recommendation, Level C evidence). Rehabilitation management plans for sitters can be further refined in the future depending on whether the ability to stand is retained.

6.4.2.4. Rehabilitation management of walkers

The Definition of walkers is that they can walk more than 10 meters independently, usually including milder type 3 and 4 SMA patients. In walkers, there is typically a greater loss of muscle strength in the lower limbs compared to the upper limbs, and the proximal muscle strength is weaker than the distal part. Studies have shown that SMA patients usually experience more severe weakness in the triceps and deltoid muscles as compared to the biceps brachii. Moreover, the gluteus maximus, the iliopsoas, quadriceps, and gluteus medius muscles are weaker in contrast to the hamstrings. [40] This difference is more noticeable in walkers who have strong muscles and can move effectively.

(1) Body positioning and posture control.
Walkers can complete most of their movements independently, having no difficulty maintaining and changing postures. Therefore, in daily posture control, the emphasis should be placed on improving the patient's endurance while sitting, standing, and walking. In addition, patients may still experience reduced proximal muscle strength in their lower limbs. Therefore, they should be mindful of their balance and coordination when walking and standing.
(2) Joint stretching and range of motion maintenance.
Focus should be placed on the limbs of walkers with reduced muscle strength to prevent joint contracture caused by insufficient activity. Passive stretching training can be reduced for joints that move autonomously, while active auxiliary training can be increased. Joints can be trained in the full range of motion under the guidance of others. Walkers can control their trunk posture, which eliminates the need for thoracolumbar braces during walking which may interfere with their natural walking posture. However, they can wear braces to adjust their sitting posture when necessary.
(3) Active movement ability and daily function.
Regular aerobic training, including muscle strength, daily movement, endurance, and balance training, is recommended for walkers and their families under professional supervision. [39] Water-based movement, centrifugal and centripetal training, and static exercises can also be employed. To control the intensity of exercise, it is recommended to keep the patient's heart rate slightly below the target heart rate. Professional institutions can determine exercise intensity by observing the patient's heart rate during exercise, especially 1 minute before the anaerobic threshold or at 40%-60% of peak oxygen uptake. Patients with limited conditions can adopt a more conservative estimation strategy at home. Typically, physical signs such as mild sweating and slightly faster breathing that doesn't interfere with communication are taken as targets for training, with the recommended training frequency being 3 to 5 times weekly. [41]

Recommendation: Walkers should insist on active movement training, which can enhance cardiopulmonary function, increase endurance, and improve posture (Class II recommendation, Level D evidence).

(This part was written by Guangyu Zhang.)

6.5. Respiratory management

The respiratory system is often affected in SMA, leading to disability and even mortality. Most of the evidence for respiratory management of SMA pertains to infants, children, adolescents, and adults. Not all patients develop respiratory failure in the early stages of the disease, so early detection of respiratory complications is crucial. Since adolescents and adults with SMA are mainly SMA types 2 to 4, this guideline mainly refers to the guidelines for respiratory management in children and evidence from adolescent and adult patients with SMA types 2 to 4.

6.5.1. Changes in respiratory physiology and respiratory complications of SMA

The primary impact of SMA on the respiratory system is the weakness of respiratory muscles, predominantly affecting the expiratory and intercostal muscles, with the diaphragm being less affected. The changes in respiratory physiology and respiratory complications mainly include: ① Respiratory muscle weakness leads to insufficient ventilation, causing hypercapnia, leading to morning headaches, fatigue, daytime drowsiness, and even respiratory acidosis and pulmonary encephalopathy; ② Respiratory muscle weakness leads to cough disorder, causing poor clearance of lower

respiratory tract secretions; ③ Recurrent respiratory tract infections can aggravate muscle weakness and cause bronchiectasis; ④ Swallowing dysfunction and gastroesophageal reflux, coupled with ineffective coughing, may lead to Aspiration pneumonia; ⑤ Weakness of the upper airway muscles causes the upper airway prone to collapse, leading to sleep-disordered breathing and decreased blood oxygen saturation at night; ⑥ Paradoxical breathing leads to underdevelopment of the chest wall and lungs; ⑦ Progressive scoliosis causes thoracic deformity, further restricting ventilation. [42-43] The interaction of these pathophysiological changes makes SMA patients prone to chronic respiratory failure, requiring non-invasive ventilation or even tracheotomy and invasive mechanical ventilation. Acute respiratory failure can occur due to acute respiratory tract infection or poor sputum drainage.

The changes in respiratory physiology and clinical manifestations of SMA vary according to the type of SMA. Infant-onset type 1 SMA which occurs within the first 6 months of life, is the earliest and most severe type, with patients dying of respiratory failure within 2 years of age. Adolescent and adult SMA patients are mainly SMA2-4 types. Type 2 SMA typically presents between 6 and 18 months of age, with noticeable weakness in the proximal muscles, and lower limbs heavier than upper limbs. As the disease progresses, complications such as dysphagia, weak cough, respiratory insufficiency, scoliosis, and joint contracture may occur. With age, the ability to sit independently is slowly gained and lost later. Life expectancy can reach 25 years, with respiratory failure the main cause of death due to progressive respiratory muscle weakness. [44] The activities of daily life can be affected in some type 3 SMA patients due to scoliosis and respiratory insufficiency. Research reports that 39% of type 2 SMA patients and 9% of type 3 SMA patients require non-invasive ventilation at a median age of 5.0 and 15.1 years. [45] Type 4 SMA is the mildest type, with onset in adulthood and mild respiratory involvement.

6.5.2. Respiratory function assessment

6.5.2.1. Clinical manifestations and physical examination

Aside from regular examinations, it's important to ask patients if they're experiencing any respiratory symptoms such as fever, cough, sputum, dyspnea, or easy choking. It's also important to inquire about the strength of their cough, whether their dyspnea is related to posture, if they have had any respiratory tract infections, and if they have lower limb edema. Additionally, it's crucial to ask if they have symptoms of sleep apnea such as difficulty falling asleep due to breathing issues, waking up frequently during the night, snoring, headaches at night and in the morning, fatigue, and daytime sleepiness. In addition to regular check-ups, a physical examination must also observe the patient's respiratory rate and breathing pattern (diaphragmatic breathing or thoracic breathing), whether there is any paradoxical breathing, any signs of retractions, scoliosis, or chest abnormalities.

Recommendation: Assessment of respiratory symptoms and physical signs should be performed routinely in adolescents and adults with SMA (Class II recommendation, Level C evidence).

6.5.2.2. Pulmonary function assessment

FVC is a crucial indicator for monitoring pulmonary function in neuromuscular diseases. Patients with SMA type 1 and some SMA type 2 tend to have considerably lower FEV1, FVC, and vital capacity at the onset of the disease. [46] The decline in pulmonary function is more noticeable in childhood and tends to stabilize in early adulthood. An eight-year retrospective study discovered that for those with SMA type 2 and some type 3, their FVC decreased by 4% to 6% each year before the age of 13, and then slowed down after that age. [45] However, patients with late-onset SMA (types 3b and 4) typically have stable lung function throughout their lives, with only a few minor exceptions.

Reduced FVC is associated with an increased risk of respiratory complications. A study suggests that when the FVC of patients with Type 2 SMA decreases to 30% of the expected value, the risk of respiratory complications significantly increases. Patients with FVC less than 20% are more likely to face respiratory complications, while patients with FVC greater than 60% have a low risk of hypoventilation at night. [42]

Pulmonary function evaluation should be carried out for sitters. SMA manifests as restrictive ventilatory dysfunction, with decreased FVC and FEV1, normal FEV1/FVC, reduced total lung volume and PEF.

Recommendation: Pulmonary function monitoring should be performed routinely in adolescents with SMA, especially in type 1 and type 2 SMA (Class I recommendation, Level A evidence).

6.5.2.3. Assessment of respiratory muscle strength

SMA primarily affects the intercostal muscles causing expiratory weakness, while diaphragm function remains relatively unaffected. Respiratory muscle weakness is associated with reduced lung compliance, lung hypoplasia, and diminished ability to cough, which may ultimately lead to chronic respiratory failure. A study has shown that patients with SMA-1c to SMA-3a exhibit decreased maximum expiratory pressure (PEmax) and maximum peak inspiratory pressure (PImax), with PEmax a sensitive indicator of respiratory muscle weakness. [47]

For neuromuscular patients aged 12 years and above, peak cough flow (PCF) is a crucial index of effective airway clearance. PCF less than 270 L/min indicates ineffective coughing, with PCF even lower than 160L/min in type 1 and most type 2 SMA patients. Since a low PCF is associated with an increased risk of respiratory infections, it can be used as an indicator for evaluating and monitoring respiratory function in SMA patients.

Recommendation: SMA often manifests as decreased PImax and PEmax, with PEmax more affected. PCF can be used as an index for effective airway clearance (Class I recommendation, Level B evidence).

6.5.2.4. Assessment for sleep-disordered breathing

The early sign of decreased respiratory function in neuromuscular diseases is sleep-disordered breathing, especially in SMA patients no matter their type. Therefore, it is essential to monitor breathing during sleep, with early detection and treatment reducing complications. In the early stage, sleep-disordered breathing may only occur during the rapid eye movement (REM) phase. In children with SMA, it manifests as sleep hypoventilation and central sleep apnea (CSA). [48] There is limited research on sleep-disordered breathing in adult patients with SMA, most of which are obstructive sleep apnea (OSA) in type 3 SMA. In addition, obese SMA patients need to be wary of coexisting OSA.

The British Thoracic Society recommends assessment for sleep-disordered breathing at least once a year in children with neuromuscular disease with vital capacity less than 60% predicted, diaphragmatic weakness, or symptoms of OSA or hypoventilation. [49] Daytime pulmonary function correlates poorly with nocturnal hypoxia and hypoventilation, [50] so assessment for sleep-disordered breathing should be routinely performed. Polysomnography (PSG) should be performed every six months to one year to guide further treatment in adolescent and adult SMA patients with uncertain disease progression, recurrent infections, or sleep-disordered breathing.

Assessment for sleep-disordered breathing includes different levels, with PSG being the gold standard. It can detect an early nocturnal decrease in arterial oxygen saturation, mainly in the REM phase. PSG can also differentiate CSA and OSA. In medical institutions where PSG is unavailable, overnight pulse oximetry can be used to screen for sleep-disordered breathing under the interpretation of an experienced respiratory physician.

If hypoxemia persists during sleep, sleep hypoventilation caused by muscle weakness (PaCO2 ≥45 mm Hg) should be alerted. Arterial blood gas analysis in the awake state should be performed to determine whether there is a hypercapnia. If possible, non-invasive carbon dioxide monitoring equipment (end-tidal CO2 monitoring or transcutaneous CO2) can be used to determine whether sleep hypoventilation exists.

If patients experience persistent hypoxemia during sleep or simple sleep hypoventilation, non-invasive positive pressure ventilation (NIPPV) should be implemented during sleep. Assessment for sleep-disordered breathing should be used to determine the optimal pressure level. [51-52]

Recommendation: Regular assessment for sleep-disordered breathing should be performed in adolescents and adults with SMA. PSG should be performed if recurrent infections or sleep symptoms occur (Class II recommendation, Level B evidence).

6.5.2.5. Chest imaging

If symptoms of respiratory infection such as fever, cough, sputum, or choking occur, it is recommended to have a chest X-ray or chest CT to detect pulmonary infection, atelectasis, and bronchiectasis. The use of diaphragm ultrasound is gaining more attention in neuromuscular diseases. Diaphragm ultrasound is recommended in patients with severe hypoventilation or hypoxemia to determine whether the diaphragm is involved. [53-54]

Recommendation: Chest imaging should be promptly performed for adolescent and adult SMA patients with recurrent infections and sleep symptoms. In routine SMA assessment, diaphragm ultrasound can indicate whether the diaphragm is involved (Class II recommendation, Level C evidence).

6.5.2.6. Functional assessment outside the respiratory system

SMA patients are also prone to swallowing dysfunction and gastroesophageal reflux, easily leading to choking and aspiration pneumonia. For a more detailed evaluation, please refer to the Gastroenterology section (subsequent report in this publication). In addition, attention should be paid to the impact of scoliosis on the respiratory system in adolescent SMA patients. For a more detailed evaluation, please refer to the Orthopedic Management (subsequent report in this publication).

6.5.3. Respiratory management of SMA

6.5.3.1. Airway clearance

In the respiratory management of SMA, it is important to clear the airway secretions to maintain airway patency. Inhalation therapy, including mucolytic agents, hypertonic saline, and bronchodilators, may be beneficial in promoting airway clearance.

In neuromuscular diseases with weak coughs, especially in patients with recurrent respiratory infections, routine airway clearance techniques are particularly important. Common methods are postural drainage, chest physiotherapy, and negative pressure suctioning through the mouth or nose or even bronchoscopy when necessary.

In SMA patients, strengthening coughing to improve PCF is a crucial airway clearance technique for children, but limited evidence exists for adults.

In adult and adolescent SMA patients older than 12 years old, methods to strengthen coughing are recommended to improve PCF when PCF is less than 270 L/min, including artificial assisted coughing and lung expansion therapy.

Artificially assisted coughing means that the therapist holds the patient's abdomen with his hand when the patient coughs and applies upward pressure to move the diaphragm upward to increase the expiratory airflow. The lung expansion therapy is to use a lung volume supplement device with a one-way valve to increase the inspiratory volume. Cough assist device (mechanical insufflation-exsufflation, MI-E) is recommended to improve PCF if it cannot reach 270 L/min, while follow-up can continue if PCF reaches 270 L/min. [42, 55]

In patients with ineffective airway clearance or persistent atelectasis on airway clearance techniques, chest wall oscillation technology, such as high-frequency chest wall oscillation or intrapulmonary oscillation ventilation, can be considered. [49] In acute respiratory infections, MI-E can assist in airway clearance to reduce the need for intubation and mechanical ventilation.

Recommendation: In adolescents and adults with SMA, inhalation therapy and airway clearance techniques should be actively used (Class II recommendation, Level C evidence).

6.5.3.2. Ventilatory support

Ventilatory support can alleviate the hypoventilation symptoms of SMA patients, reduce respiratory infections and hospitalization rates, improve the quality of life, and prolong survival.

(1) Non-invasive positive pressure ventilation.
For patients with sleep-disordered breathing or nocturnal hypoventilation, ventilatory support should be started at an appropriate time. In neuromuscular diseases, NIPPV is the first choice, where a comfortable mask or nasal mask can be chosen with bilevel positive airway pressure (BPAP). NIPPV allows the respiratory muscles to rest while correcting hypercapnia and hypoxemia.
In the early stages of the disease, BPAP is indicated in patients with nocturnal hypercapnia and hypoxia during sleep, while patients developing type II respiratory failure require BPAP throughout the day. The timing of NIPPV is shown in Table 2. According to foreign guidelines for respiratory management in children with type 2 SMA and recommendations for non-invasive ventilation in patients with neuromuscular diseases, [42, 56] this guideline summarizes the timing of NIPPV in adolescent and adult SMA patients, as shown in Table 2. Research has also shown that among neuromuscular patients with FVC less than 50%, 70% will require NIPPV within one year, even if there are no symptoms of nocturnal hypoventilation. [57]

Indications	Timing
Either condition warrants consideration of initiation of nocturnal NIPPV therapy.	Daytime hypercapnia (PaCO2 >45 mm Hg) Sleep-disordered breathing (including sleep hypopnea, OSA, and CSA) Paradoxical breathing Orthopnea Recurrent pulmonary infections requiring hospitalization (>3 times/year)
For those who have been treated with nighttime NIPPV, daytime NIPPV treatment is required at the same time if this happens.	The time required for NIPPV extends to the awake state Swallowing disorders due to dyspnea, relieved by NIPPV Severe dyspnea and unable to speak in full sentences Hypoventilation with daytime lowest SpO2 <95% or/and awake PaCO2 > 45 mm Hg

Table 2. Timing of the application of non-invasive positive pressure ventilation.
NIPPV: non-invasive positive pressure ventilation therapy; PaCO2: partial pressure of carbon dioxide in arterial blood; OSA: obstructive sleep apnea; CSA: central sleep apnea; SpO2: blood oxygen saturation.

The setting of the ventilator should be determined by a respiratory physician based on the patient's clinical symptoms, arterial blood gas analysis results, ventilation, and assessment of sleep-disordered breathing. If possible, it is recommended to optimize ventilator settings and mask under PSG with transcutaneous CO2 results, which can also detect leaks early. Besides, the side effects of non-invasive ventilation should be noted such as abdominal distension, aspiration, and skin pressure injury. [52] The airway should be humidified during NIPPV.

After commencing NIPPV, assessment for sleep-disordered breathing and CO2 concentration and arterial blood gas analysis should be reviewed to confirm its effectiveness, readjusting settings when necessary. Regular follow-ups should be carried out to review the condition of sleep-disordered breathing and early detect hypoventilation.

(2) Mechanical Ventilation.

Due to the effectiveness and widespread use of non-invasive ventilation, tracheostomy is rare in SMA patients. Tracheotomy followed by mechanical ventilation may be required under the following circumstances: ① Severe bulbar paralysis; ② Inability to extubation within two weeks; ③ NIPPV failure or intolerance; ④ Spontaneous breathing trials less than 30 minutes; ⑤ Ineffective airway clearance on mechanically assisted coughing. Mechianical ventilation should be individualized based on clinical status, prognosis and quality of life after discussion with the patient and family. Informed consent is required.

Recommendation: Elective home non-invasive BPAP should be employed among adolescent and adult SMA patients with nocturnal hypoventilation or sleep-disordered breathing to correct hypercapnia and hypoxemia while resting the respiratory muscles. Some patients who cannot be treated with non-invasive ventilation can consider invasive mechanical ventilation (Class I recommendation, Level B evidence).

(3) Oxygen therapy.

Since hypoxemia in SMA patients is mostly accompanied by hypoventilation, oxygen therapy may further aggravate CO2 retention, leading to severe respiratory acidosis. For SMA patients with hypercapnia who require oxygen therapy, it should be given during non-invasive ventilation. High-flow oxygen is not recommended in patients with SMA.

Recommendation: Oxygen therapy may aggravate CO2 retention in adolescents and adults with SMA. The timing and implementation method of oxygen therapy should be determined based on clinical conditions (Class II recommendation, Level C evidence).

(4) SMA complicated by acute respiratory failure.
Acute respiratory failure is mostly caused by respiratory infection. There is limited evidence for the treatment of acute respiratory failure in SMA patients. The main treatments include anti-infection and airway clearance, with non-invasive ventilation being the first choice for respiratory support. The selection of antibiotics is based on age and comorbidities, together with clinical conditions under the guidelines for respiratory infections in children and adults. Antibiotics should cover the spectrum of anaerobic bacteria. Invasive ventilation should be considered for patients who cannot maintain non-invasive ventilation due to difficulty in sputum drainage or those who are comatose.
(5) Reduce aspiration and deal with gastroesophageal reflux. Refer to the Gastroenterology section for details (subsequent report in this publication).
(6) Breathing exercises, surgery for scoliosis correction, and nutritional support are all closely related to respiratory management. Refer to the other section for details (subsequent report in this publication).
(7) Vaccination.
Respiratory infection is common in SMA adolescents, and annual influenza and pneumococcal immunizations are recommended.
(8) Effects of DMT on the respiratory system in SMA.
Evidence shows that nusinersen can improve pulmonary function and sleep-disordered breathing in children with SMA after 1 year of treatment. [58] It has also been found to improve 6MWT and PCF in adult patients with type 3 SMA. [59] However, after one year of DMT, only a small fraction of SMA patients treated with mechanical ventilation or non-invasive ventilation will be weaned from the ventilator or require less ventilator time per 24 hours. More data are needed to clarify the effectiveness of nusinersen.
Risdiplam has been confirmed to improve motor function in type 2 and non-ambulatory type 3 SMA. [60] There is limited evidence of its impact on the respiratory system in adolescent and adult SMA patients.

(This part was written by Jinmei Luo and Yi Xiao.)

6.6. Anesthesiology management

6.6.1. Ultrasound-assisted localization and real-time guidance of intrathecal injection

(Note: Depending on the situation of different hospitals, the ultrasound-guided intrathecal injection can be performed by the anesthesiology department, ultrasound department or other departments.)

Nusinersen is the world's first approved gene therapy product for SMA. Since it cannot pass the blood-brain barrier, it must be administered through subarachnoid injection. [61] However, adolescent or adult SMA patients usually have more severe spinal deformities due to muscle weakness. Hence, blind punctures with traditional anatomical landmark are complex and risky. Although foreign studies have reported that X-rays and CT can guide lumbar or cervical intrathecal injection in such patients, the potential harm of cumulative radiation exposure cannot be ignored due to the need for repeated administration. [62] In addition, infants and young children with SMA can now use nusinersen earlier. Although such children usually do not have severe spinal deformities, accurately locating the puncture point and estimating the puncture depth is still of great clinical significance for the safe and effective intrathecal injection. Ultrasound has the advantages of visualization and no radiation exposure. This technology can identify the puncture point and estimate the depth needed. Moreover, it provides real-time guidance during the procedure, thereby minimizing damage to surrounding organs and blood vessels and providing safe intrathecal injection. [63-64] This guideline summarizes the application of ultrasound-assisted localization and real-time guidance technology in intrathecal injection of SMA patients for reference by clinical physicians. This guideline aims to improve the safety and accuracy of intrathecal injection of SMA patients and avoid repeated radiation exposure. It is not mandatory and should not be used to determine medical liability.

6.6.1.1. Preoperative spinal imaging

(1) CT examination.
CT can observe the entire vertebral bodies and accessory bone structures. Three dimensional CT(3D-CT) can fully display the structure of

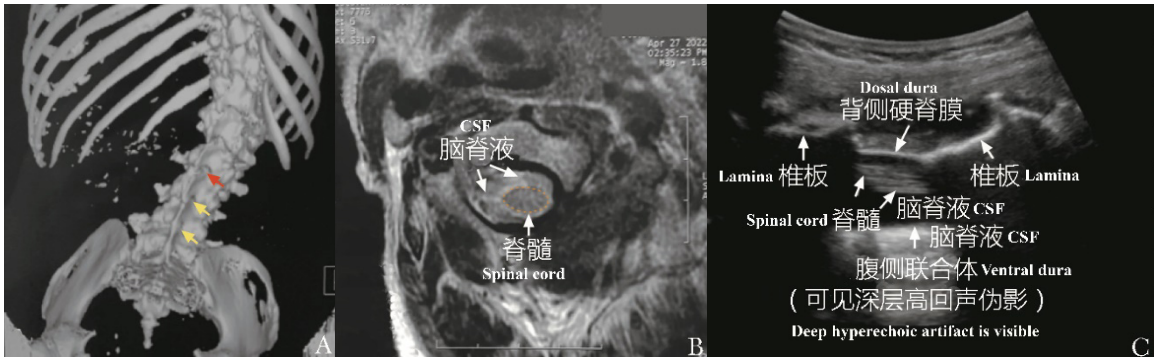

Figure 1. Preparation of imaging studies before intrathecal injection. A. 3D-CT imaging of the spine in an SMA patient shows interspinous space with relatively wide interlaminar space (red arrow), and disappeared interspinous space due to bony fusion (yellow arrows) with narrow interlaminar space. B. MRI T2-weighted imaging of the C1-C2 intervertebral space in an SMA patient shows the spinal cord (within the orange dashed line) displaced to the right side of the spinal canal. C. Ultrasound imaging of an SMA patient via the paramedian sagittal oblique L2-L3interlaminar approach, shows the medium to high echogenicity spinal cord in the subarachnoid space.

the spine, which can provide not only information about overall scoliosis and local vertebral rotation but also detailed information about the local space size of the puncture target, such as the interspinous space, interlaminar space and intervertebral foramen (Fig. 1A). [65] It can determine any puncturable space and complete assessment before puncture based on the size of the puncturable space, calcification of the surrounding structures, and osteophyte formation. [65] However, since the image is reconstructed, the detailed information may deviate from the actual situation.

(2) MRI examination.

MRI is recommended to evaluate soft tissues. [65] In SMA patients with spinal deformity, although sagittal MRI images cannot show the continuous anatomical structure of the spine, they can still be used to preliminarily assess the depth of the target puncture site from the skin. The transverse axial images can show the cross-sectional morphology and signal intensity of the spinal cord, cauda equina, CSF, dura mater, and epidural space, providing more detailed information for clinical decision-making (Fig. 1B). On T1-weighted images, the spinal cord has an intermediate signal intensity, the CSF has a low signal intensity, and fat in the epidural space has a high signal intensity. The contrast between the CSF and epidural space signals is relatively high. On T2 fat-suppressed weighted sequences, the spinal cord has an intermediate signal intensity; the CSF and epidural space have high signal intensity, with relatively high contrast between the CSF and spinal cord signals. [65] Whenever possible, the segment with normal spinal cord or cauda equina morphology and clear and uniform CSF signals should be selected for puncture. SMA patients may have the following conditions due to developmental abnormalities and anatomical malformations: ① Subarachnoid obstruction or incomplete obstruction manifests as thickening of the proximal cauda equina, narrowing of the subarachnoid space, and abnormal or unclear CSF signals. Such segments should be avoided for puncture, as they increase the risk of damaging the spinal nerves during puncture and may cause poor CSF return, affecting further drug injection. ② Lower-located conus medullaris (below the L1-L2 level). The distal spinal segment to the conus medullaris should be selected for puncture if possible. ③ the spinal cord deviates from the center (mainly on the concave side of the scoliosis). [66] If this situation exists in the pre-selected puncture segment, the side of the spinal cord that is relatively distal from the dura mater should be selected for puncture to avoid damage to the spinal cord due to the small puncture space (Fig. 1C). In addition, when there are tumors, cysts, inflammation, or deformities in the spinal canal, the spinal cord and cauda equina may also have abnormal appearance or abnormal signals, which should be carefully evaluated and identified before the procedure. It is strongly

recommended that adolescent and adult SMA patients undergo routine MRI examinations before the procedure. However, due to the long time it takes to acquire MRI images, it may not be suitable for infants and preschool SMA patients who cannot cooperate. The preoperative evaluation of such children may rely more on physical and ultrasound examinations (see below for details).

(3) Ultrasound examination.

Ultrasound can be used to guide real-time intrathecal injection and plays a vital role in pre-puncture assessment, including: ① Evaluate the extraspinal conditions. Under ultrasound, the bone and dura mater are highly echogenic. When the ultrasound probe scans the interspinous or inter-laminal space, the "double-track sign" of the high echo of the dura mater indicates a puncturable space. Otherwise, it indicates that the shallow layer of the space may be surrounded by ossified soft tissue or osteophytes, where the ultrasound beam cannot be projected, making it difficult to puncture. In addition, ossified structures or osteophytes may be located in the puncture path, affecting the direction and angle of needle insertion, which requires careful evaluation before puncture. ② Assess the intraspinal conditions. Under ultrasound, the CSF is anechoic, and the spinal cord/cauda equina is medium-to-high echoic. If medium-to-high echo structures are mixed in the anechoic CSF, they should be avoided during the puncture process, or other segments should be selected (Fig.1B). ③ Locate the puncturable segment. Under ultrasound, the morphology of the sacral and lumbar bones is distinct. The scan can be started from the sacrum. After determining the L5-S1 intervertebral space, further scan toward the head and locate each spinal cord segment one by one. [67] ④ Measure the puncture depth. It is mainly used to estimate the puncture depth in patients with type 3 SMA or infantile SMA who do not have obvious spinal deformities. Usually, a cross-sectional scan is performed in the interspinous space of the target puncture segment to measure the depth from the skin to the dura mater, guiding the blind puncture. [68]

In addition, ultrasound pre-scanning is an essential means of evaluation before puncture for infants and children who cannot cooperate with CT and MRI examinations.

Recommendation: Based on clinical practice experience, adolescent and adult SMA patients should undergo routine CT and MRI examinations before puncture, and the puncture conditions should be further evaluated during the ultrasound pre-scan. It is not mandatory for infants and young children to undergo CT and MRI examinations before puncture, and ultrasound pre-scans can be used to evaluate the puncture conditions (Grade II recommendation, Level D evidence).

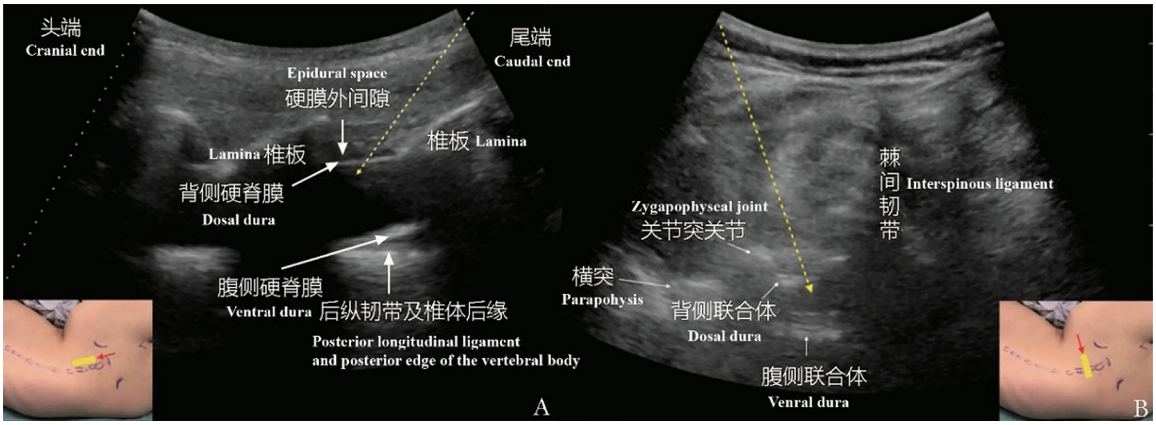

Figure 2. Images of real-time ultrasound guiding lumbar puncture. A. Position of the ultrasound probe and ultrasound image for real-time intrathecal injection guidance via a paramedian sagittal oblique interlaminar approach. B. Position of the ultrasound probe and corresponding ultrasound image for real-time intrathecal injection guidance via a transverse interlaminar approach. The yellow rectangular blocks represent the probe position, the red arrows indicate the needle direction, and the yellow dashed lines with an arrow indicate the needle path.

6.6.1.2. Preparation of Ultrasound-guided intrathecal injection in SMA patients

Equipment: Ultrasound equipment with good imaging quality, with convex probes for adolescents or adult patients and linear probes for infants and children. Sterile conditions:

The puncture site should be routinely disinfected with alcohol, or iodine twice and covered with a sterile drape. If conditions permit, the operator should wash hands and wear surgical gowns and sterile gloves to complete the procedure. If ultrasound real-time guidance is used for puncture, the ultrasound probe and wire should be covered with a sterile probe cover. Puncture needle: Use a 19-25 G lumbar puncture needle with a core stylet for puncture and a needle compatible with ultrasound should be selected for ultrasound-guided procedure. [63, 69] Injection procedure: After the needle has entered the subarachnoid space, the stylet is pulled out. If there is no blood return and the CSF flows freely, nusinersen may be administered slowly. Should blood reflux occur or if CSF flow is obstructed, it is necessary to reposition the needle or alter the puncture site to ensure both the absence of blood reflux and unimpeded CSF flow before proceeding with the injection. It is not recommended to withdraw CSF by negative pressure suction when the CSF return is impeded.

6.6.1.3. Technology of Ultrasound-guided intrathecal injection in SMA patients

(1) Ultrasound-assisted localization of intrathecal injection technology.
If the patient is suitable for vertical puncture through the interspinous space based on pre-puncture assessment, the intrathecal injection can be completed under ultrasound-assisted localization. [68] The patient is positioned in a upright or lateral decubitus position. Place a low-frequency convex or high-frequency linear probe (suitable for infants or children) in a transverse plane over the vertebral bodies. Slide the probe from the sacral level, along the median crest towards the head to locate the L5-S1 intervertebral space. Following this, scan the L2-L5 lumbar intervertebral spaces to identify an optimal puncturable space where both the ventral and dorsal dura mater are visible. Measure the depth from the skin to the dorsal dura mater at this selected space to determine the appropriate puncture depth. Simultaneously, assess the presence of any axial rotation of the vertebral body and the rotation angle to guide the direction of the needle insertion. Especially in cases where the rotation angle is significant, it is recommended to carry out the puncture under real-time guidance to ensure precision and safety. After the puncture point is marked on the body surface, the blind intrathecal injection can be completed under sterile conditions. [68]

Recommendation: For patients with no severe spinal deformity who can receive complete blind intrathecal injection, it is recommended to use ultrasound to assist in locating the puncture point and estimating the puncture depth before puncture (Grade II recommendation, Level B evidence).

(2) Ultrasound-guided real-time intrathecal injection. It can be divided into the following 4 types:
① Ultrasound-guided real-time intrathecal injection through the paramedian sagittal oblique lumbar interlaminar approach. For SMA patients with significant spinal deformities, intrathecal injection via the paramedian sagittal oblique interlaminar approach is highly recommended. Before proceeding with the puncture, it's essential to carefully review 3D-CT and MRI scans to identify suitable puncture space characterized by ample space, sufficient subarachnoid CSF, and minimal puncture depth. During the procedure, the patient should be positioned comfortably on their side. Slide a low-frequency convex probe from the sacral level along the median sacral crest upwards to locate the L5-S1 intervertebral space first. Following this, scan each spinal segment towards the head, identifying and marking each spinous process on the skin. Connect these markings to guide the probe placement along the longitudinal axis of these connected lines. Move the probe laterally until a continuous high-echo structure with a "horse head sign" is observed on the ultrasound. Tilting the probe inward, scan until the high-echo lamina continuity is interrupted, indicating the interlaminar space. The ultrasound will display the ventral and dorsal dura mater arranged parallel within this space, giving the "double track sign". [69] Adjust the probe carefully to ensure the preferred puncture site has a clear image, characterized by a favorable needle insertion angle, absence of obstructive bone spurs, and no

mixed echo structures in CSF. The intrathecal injection can be conducted under sterile conditions through the longitudinal sagittal oblique approach.

Recommendation: For patients with severe spinal deformity on imaging, it is recommended that the paramedian sagittal oblique interlaminar approach be used to complete ultrasound-guided intrathecal injection (Grade I recommendation, Level A evidence).

② Ultrasound-guided intrathecal injection via the transverse lumbar interlaminar approach. When the interlaminar space is accessible for puncture but the standard paramedian sagittal oblique lumbar interlaminar approach proves impractical (e.g., the patient can only be positioned in the right side decubitus position, making it challenging for a right-handed practitioner to insert the needle from the caudal to the cephalad end), an alternative method involving transverse interlaminar intrathecal injection may be utilized. [70] For this technique, place a low-frequency convex probe in the transverse plane, centering the probe over each spinous process. Move the probe from the caudal end towards the cephalad end to identify a space that displays distinct ventral dura mater and visible no mixed echoic CSF on the ultrasound, which is then selected as the optimal site. The side with no obstructive bone spurs is chosen for needle insertion. The entire puncture procedure is conducted under sterile conditions, with the needle inserted adjacent to the outer side of the probe, moving towards the inner side.

Recommendation: For patients with spinal deformity on imaging, when the paramedian sagittal oblique interlaminar approach is difficult to puncture, a transverse interlaminar approach can be attempted to complete the intrathecal injection under real-time ultrasound guidance (Grade IV recommendation, Level D evidence).

③ Ultrasound-guided intrathecal injection through longitudinal lumbar transforaminal approach. When encountering difficulties with lumbar interlaminar space punctures due to reasons such as pre-operative assessments not identifying a viable puncture space or the actual puncture being hindered by a narrow interlaminar space, intrathecal injection through the lumbar intervertebral foramen becomes a viable alternative. It's essential to review the patient's 3D-CT images, focusing on the lumbar convex side lamina and the openings of the lumbar intervertebral foramen. Additionally, examining the cross-sectional and coronal CT images to understand the spatial relationships with adjacent critical organs and soft tissues is crucial. The puncture route must avoid the lumbar nerve exit, typically situated in the upper third of the intervertebral foramen. The patient is positioned in a lateral decubitus position, with the lumbar convex side facing upwards. Place a low-frequency probe over the lumbar intervertebral foramen on the convex side and scan longitudinally to reveal the upper and lower lumbar pedicles as highly echogenic with an acoustic shadow beneath. A "double track sign," indicative of the dura mater, appears as a parallel high-echo short line between the pedicles, with the echo-free subarachnoid space between these lines. The puncture is performed under sterile conditions, adopting a technique that involves inserting the needle from the caudal to the cephalic end, aiming to keep the needle path as close as possible to the subsequent lumbar pedicle to access the intervertebral foramen and delicately pierce the dura mater. Throughout this procedure, the patient must remain conscious and promptly report any discomfort, particularly electric shock-like feeling in the thigh, which may occur if the needle tip contacts a nerve root. Should the needle touch a nerve root or blood is aspirated, the procedure must be paused immediately to readjust the needle's angle before cautiously proceeding.

Recommendation: For patients with spinal deformities identified through imaging and who experience difficulties with punctures via the paramedian sagittal oblique or transverse interlaminar approaches, the longitudinal lumbar transforaminal approach is recommended under real-time ultrasound guidance (Grade IV recommendation, Level D evidence).

④ Ultrasound-guided intrathecal injection through the transverse approach to the atlantoaxial interlaminar space. When facing challenges in performing punctures through various lumbar approaches, the cervical interlaminar approach

can be considered, specifically after a thorough re-evaluation. [71] For several key reasons, the atlantoaxial intervertebral space is often recommended. Firstly, this space is generally wider than other cervical intervertebral spaces, providing easier access. Secondly, the space between the spinal cord's boundary and the dura mater in this area is relatively more extensive, reducing the risk of the puncture needle causing any damage to the spinal cord, which makes the procedure notably safer. [72] Before proceeding with this technique, it's essential to carefully analyze the cervical 3D-CT imaging data, focusing on the posterior intervertebral space of the atlantoaxial vertebra. Additionally, examining cervical MRI images can offer insights into the spinal cord's morphology and determine the distance between the spinal cord boundary and the dura mater, allowing the selection of the puncture side with a more favorable distance, enhancing safety. The patient should be in a lateral decubitus position, with the side to be punctured facing upwards. Place a low-frequency convex probe in a transverse plane to scan the C1-C2 intervertebral space to plan the needle insertion route meticulously. Employing color Doppler ultrasound helps identify the vertebral artery location, ensuring the planned puncture path avoids it. The procedure is conducted under sterile conditions and demands careful needle insertion from the outside in. Given the thicker nature of the dura mater at the atlantoaxial intervertebral space compared to that in lumbar regions, the needle should be advanced slowly to prevent it from inadvertently entering the subarachnoid space and potentially contacting the spinal cord.

Recommendation: For patients whose spinal deformities make lumbar punctures particularly challenging by imaging, the transverse approach through the atlantoaxial interlaminar space is recommended under real-time ultrasound guidance (Grade IV recommendation, Level D evidence).

6.6.1.4. Clinical decision-making of ultrasound-assisted/guided intrathecal injection for SMA patients

For SMA patients with different conditions, the clinical decision-making flowchart for ultrasound-assisted/guided intrathecal injection is shown in Fig. 3.

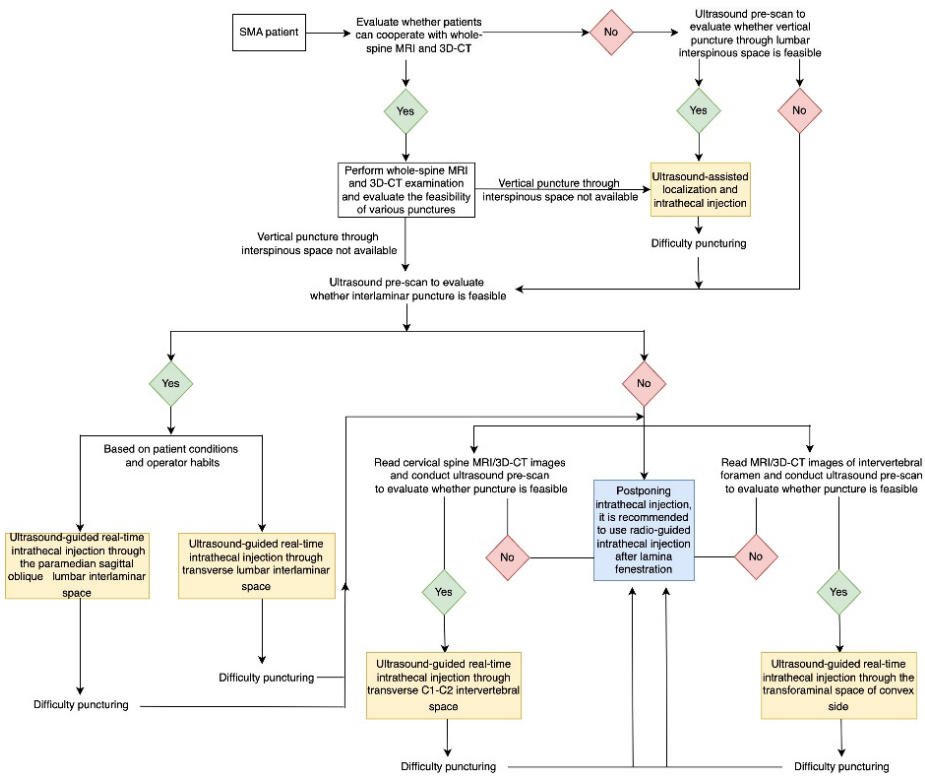

Figure 3. Clinical decision-making process of ultrasound assisted/guided intrathecal injection.

(1) Adolescents and adults with SMA and severe spinal deformity.

Type 1 and type 2 SMA patients have early disease onset, so most of them have severe spinal deformities as they transition into adolescence or adulthood, requiring routine evaluation with 3D-CT and MRI imaging. Scoliosis and vertebral rotation complicate traditional vertical approaches for these patients, making it highly advisable to opt for the interlaminar approach, guided by real-time ultrasound, for intrathecal injections. In cases where the interlaminar approach is rendered impractical due to various factors-- such as the postoperative placement of lumbar spinal implants without interlaminar "fenestration" or the calcification of surrounding tissues— alternative puncture sites through the interlaminar foramen or the cervical spine should be considered. If necessary, puncture procedures can be deferred to specialists in the department of pain treatment or radiology. There, the procedure can be conducted under X-ray or CT imaging guidance or, after lumbar surgery, under real-time ultrasound guidance. It is paramount for centers to tailor their approach based on each patient's specific circumstances.

Recommendation: SMA patients with spinal deformities should undergo routine spinal 3D-CT and MRI imaging evaluation before puncture. The longitudinal sagittal oblique approach via the lumbar interlaminar space for intrathecal injection is recommended under real-time ultrasound guidance (Grade IV recommendation, Level A evidence).

(2) Adolescents and adults with SMA without severe spinal deformity.

Type 3 SMA patients usually have the onset of their disease during adolescence or adulthood, and spinal deformity might not be severe when treated with Nusinersen. Nevertheless, these patients could still exhibit mild scoliosis or vertebral rotation alongside other conditions such as ligament calcification, degenerative changes in the facet joints, and the formation of osteophytes. Therefore, intrathecal injection is recommended with ultrasound assisted or real-time guidance. The choice of the specific method should be based on the operator's judgment with the findings of imaging.

Recommendation: For patients without severe spinal deformity and a feasible midline approach to the interspinous space, the intrathecal injection should be conducted with the help of ultrasound-assisted localization (Grade III recommendation, Level D evidence).

(3) Adolescents or adults with SMA and severe obesity.

Severely obese SMA patients should undergo routine 3D-CT and MRI imaging before puncture. If the patient has no spinal deformity, the intrathecal injection can be done with ultrasound-assisted localization. [73] It is recommended to perform ultrasound before puncture to evaluate the presence of slight rotation of the vertebrae and the rotation angle, and to measure the puncture depth(Y. Li *et al.,* 2020). If the patient has a spinal deformity, the feasibility of ultrasound-guided intrathecal injection should be evaluated based on the results of 3D-CT, MRI and ultrasound pre-scanning. If it is feasible, the puncture can be completed under ultrasound real-time guidance. If it is not feasible, it is recommended that the specialists from the department of pain treatment or radiology complete the puncture under X-ray or CT guidance. A longer puncture needle should be selected if the puncture is completed under ultrasound real-time guidance. If conditions permit, an ultrasound puncture rack that matches the ultrasound probe can be used to effectively improve the success rate of the puncture.

Although ultrasound-guided puncture has many advantages over radio-guided puncture, the quality of ultrasound imaging may be affected by thick body fat in severely obese patients. Clinical decisions depend on the specific situation.

Recommendation: The strategy for intrathecal injection of adolescent or adult SMA patients with severe obesity is consistent with that of non-obese patients. Since thick body fat may affect the quality of ultrasound imaging, it is recommended to use an ultrasound puncture rack to improve the success rate of puncture when necessary (Grade II recommendation, Level C evidence).

(4) Adolescent or adult SMA patients after lumbar spinal implant placement.

Following imaging assessments before the procedure, adolescent and adult SMA patients who

have received lumbar implant placement and interbody fusion can consider ultrasound-guided intrathecal injection through the lumbar approach (including intervertebral foramen approach) if a viable path exists post-surgery. In instances where the lumbar puncture is unavailable, an alternative route through the atlantoaxial intervertebral space may be considered after thorough evaluation under ultrasound guidance. The Peking Union Medical College Hospital orthopedic team has innovated a technique specifically for SMA patients undergoing spinal correction surgery. This technique deliberately avoids interbody fusion in certain vertebral segments, allowing a pathway available for future ultrasound-guided intrathecal injection through the lumbar approach. Should these methods prove unviable, it is advised for specialists in pain management or radiology to undertake the puncture and injection process, utilizing X-ray or CT imaging for guidance to ensure accuracy and safety.

Recommendation: For patients who have undergone lumbar implant placement, if the lumbar spine has a puncturable path, ultrasound-guided real-time intrathecal injection can be performed. Otherwise, it can be performed through the atlantoaxial intervertebral space under real-time ultrasound guidance (Grade III recommendation, Level D evidence).

(5) Infants/children with SMA.

With the inclusion of nusinersen in the national medical insurance reimbursement list in China, more infants and children with SMA can receive it in the early stages of the disease. Considering that these children are at the early phase of the disease, where spinal deformities are not yet prominent, and taking into account the potential for limited cooperation from children as well as the adverse psychological effects that CT and MRI procedures might have on them (due to their claustrophobic environments and the possible need for separation from caregivers), it is advisable to opt for ultrasound pre-scanning for pre-puncture evaluations. Ultrasound examinations not only circumvent the drawbacks associated with CT and MRI but also benefit from the incomplete ossification of the spinal canal's posterior structure in infants and young children, providing an excellent acoustic window for the ultrasound. Moreover, the relatively shallow spinal canal depth in newborns and young children facilitates the acquisition of high-quality ultrasound images with superior resolution, enhancing the visibility of local anatomical structures. [74] In addition, since the conus medullaris is located at a low level in newborns (at the level of L2-L3 at birth and the level of L1-L2 3 months after birth) [75] and other developmental abnormalities (such as congenital spina bifida and tethered cord) may coexist, ultrasound pre-scanning is also crucial to ensure accurate and safe puncture (Muthusami *et al.*, 2017). The objective of the pre-scan is to examine the location of the conus medullaris, the shape and spread of the cauda equina nerves, and the presence of CSF in the subarachnoid space. This ensures the selection of an optimal site for puncture where the subarachnoid space is adequately filled with CSF, minimizing the risk of damaging the cauda equina nerves during the procedure. [74, 76] Medication can be administered using the median approach after identifying the ideal puncture space, accurately measuring the puncture depth, and evaluating the angle of needle insertion. Alternatively, ultrasound can guide the administration in real time through either the paramedian oblique sagittal interlaminar approach or the transverse interlaminar approach. [77]

Infants or children who are unable to cooperate should complete intrathecal injections under sedation or general anesthesia. Sedation can be achieved by target-controlled propofol infusion under bispectral index monitoring, with the effect chamber concentration between 2.0 and 3.0 μg/mL. The bispectral index value should be maintained between 45 and 60 during the operation to ensure the child does not move. [78] For newborns and children who can cooperate, it is recommended to apply local lidocaine cream to the puncture site 30 minutes before puncture before puncture.

Recommendation: If infants or children with SMA cannot cooperate consciously, CT and MRI examinations are not required. Ultrasound can be used to assess the puncture conditions, and ultrasound-assisted localization or real-time intrathecal injection can be selected based on the individual conditions of the patient and the operator's preference (Grade III recommendation, Level D evidence).

6.6.1.5. Complications and their prevention

(1) Headache after lumbar puncture.
The design elements of the needle, specifically its tip, are important factors affecting the incidence of headache after lumbar puncture. The risk is reduced when using a thin, tapered needle compared to a cutting needle. Positioning the needle tip parallel to the spine's long axis also lowers the incidence of headaches. Conversely, an increased number of puncture attempts is associated with a higher risk of headaches. [79-80] Despite common beliefs advocating for bed rest post-lumbar puncture, current data does not support that bed rest effectively reduces the incidence of post-procedure headaches. [80]

(2) Bleeding during puncture.
During lumbar puncture, the puncture needle may occasionally injure the blood vessels in the epidural space, and blood may overflow from the needle lumen after the stylet is removed. For patients with normal coagulation function, this situation rarely leads to severe consequences such as epidural hematoma. However, for patients with persistent bleeding after puncture and abnormal coagulation function or anticoagulant therapy, it is a risk factor for epidural hematoma. Management includes: ① Discuss with the neurologist the advantages and disadvantages of the procedure, and then decide whether to go ahead or not on the patient's unique circumstances. ② Due to the challenge of confirming the accurate placement of the puncture needle tip by bleeding at the initial puncture site, selecting a different site and performing a new puncture is advisable. ③ After lumbar puncture, closely observe symptoms and signs related to epidural hematoma.

(3) Spinal cord injures.
Before puncture, the MRI images should be carefully reviewed, and ultrasound pre-scans should be performed. It is preferred to avoid the puncture path involving the cauda equina, spinal cord, nerve roots, and spinal blood vessels which cause indirect spinal cord injury. Ultrasound real-time guidance can reduce the incidence of nerve injury during puncture. [81] Paresthesia during puncture indicates the possibility of nerve injury, requiring strengthened post-puncture monitoring. If the neurologist confirms that there is nerve injury, steroids, and neurotrophic drugs should be given in time to promote nerve repair. If there is space-occupying nerve injury caused by epidural hematoma or abscess, a surgical consultation should be immediately requested to confirm the diagnosis and perform surgery as soon as possible to relieve nerve compression.

(4) Epidural hematoma.
Intraspinal hematoma is a rare complication with serious consequences. Clinical manifestations include severe back pain within 12 hours of hematoma formation, followed by muscle weakness and sphincter dysfunction after a short period of time, and finally develop paraplegia. Preventive measures include gentle puncture and avoiding repeated punctures after the needle breaks through the ligamentum flavum. [81] For SMA patients with abnormal coagulation function, the patient's hemostatic status should be assessed based on indicators such as platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen quantification. An individualized choice should be made after carefully weighing the benefits and risks of intrathecal injection. The safe lower limit of platelet count for subarachnoid puncture is still unclear. It is generally believed that subarachnoid puncture is prohibited when the platelet count is less than 50×10^9/L. For patients who receive anticoagulant or antiplatelet drugs during the peri-puncture period, the principles for preventing intraspinal hematoma can be found in the "Periprocedural antithrombotic management for lumbar puncture: Association of British Neurologists clinical guideline" in 2018. [82]

(5) Infection at the puncture site.
To avoid infection at the puncture site, the principle of sterile technique should be strictly followed during the puncture process. The puncture site should be disinfected and covered with a sterile drape. The operator is required to wash hands and wear a sterile surgical gown. The ultrasound probe needs to be covered with a sterile probe cover. After the intrathecal injection, the puncture needle is removed and covered with a sterile dressing.

Recommendation: The complications and prevention of intrathecal injection in SMA patients are consistent with those of intraspinal puncture (Grade I recommendation, Level A evidence).

(This part was written by Xulei Cui.)

6.6.2. Perioperative management of scoliosis correction surgery and other surgeries

Almost all patients with type 2 and type 3 SMA will have scoliosis, often accompanied by chest deformity and respiratory system involvement. [83] Scoliosis frequently appears in early childhood, usually in the thoracolumbar segment. As the patient's ability to walk and stand declines, the progression of scoliosis can gradually accelerate. [84-85] SMA patients who are ineffective with conservative treatment and whose scoliosis progresses rapidly should be actively treated with surgical intervention. [86] SMA with scoliosis is syndromic scoliosis, and its perioperative risk is higher than that of idiopathic scoliosis. Therefore, an individualized anesthesia management plan can help patients smoothly pass the perioperative period and obtain a good prognosis based on a comprehensive preoperative assessment of the patient's cardiopulmonary function and systemic organ conditions, the severity of scoliosis, growth, and development, and nutritional, metabolic status.

Perioperative management is challenging due to the complex conditions of SMA patients and the traumatic scoliosis correction surgery with a long duration. An individualized anesthesia and perioperative management plan should be made with multidisciplinary collaboration and comprehensive assessment.

6.6.2.1. Preoperative evaluation and optimization

(1) Scoliosis.
SMA is a systemic disease, and scoliosis usually involves many vertebrae, necessitating long segments fusion and even pelvic fixation during surgery. [87] Therefore, it is crucial to gain a comprehensive understanding of the scope and severity of spinal lesions before surgery. Individualized anesthesia plans should be made based on the combination of the complexity of the procedure, its duration, and the anticipated volume of blood loss with the surgeons' communication.

(2) Airway assessment.
As the disease progresses, SMA patients may develop joint contracture and limited mouth opening, and may also be combined with cervical rotation and thoracic deformity. Individuals with halo gravity traction before surgery are at a heightened risk for encountering difficulties with tracheal intubation and mask ventilation compared to the general population. [88] Additionally, the incidence of gastroesophageal reflux is notably higher in patients with severe spinal deformities, necessitating extra precautions to prevent aspiration. The patient's airway conditions should be comprehensively assessed before surgery, including mouth opening, neck mobility, mandibular protrusion, thyromental distance, and Mallampati classification. It is also important to inquire about any history of airway management difficulties. Given that SMA patients may have severe spinal and thoracic deformities, which can lead to tracheal deviation, stretching, or even compression and stenosis, special attention is required. Considering awake intubation may be prudent for those anticipated to have challenging intubations. It is essential to discuss the process of awake intubation with the patient beforehand to ensure their cooperation and to enhance the likelihood of a successful procedure. [89]

(3) Cardiopulmonary function assessment.
The preoperative evaluation of cardiopulmonary function, especially the respiratory function, is crucial for SMA patients. These patients often exhibit chest deformities, typically associated with restrictive ventilatory impairment. The severity of spinal deformity directly correlates with the degree of impact on cardiopulmonary function. [90] Additionally, SMA patients with scoliosis often present with weak muscle strength and involvement of respiratory muscles, which further compromises respiratory function. Before surgery, it is essential to ascertain the patient's history of recurrent lung infections, the presence of sleep apnea, and the necessity for ventilatory support. In terms of examinations, tailored assessments such as ventilation function tests and blood gas analysis should be conducted based on the individual's condition. Patients should engage in guided breathing exercises. Preoperative strategies may include traction and non-invasive ventilation for those with significant respiratory dysfunction and hypoxia, with or without CO2 retention. The collaborative efforts of multidisciplinary teams encompassing orthopedics, anesthesiology, respiratory medicine, and rehabilitation medicine are pivotal in enhancing the patient's preoperative respiratory function, thereby ensuring a

safer perioperative period. Regarding cardiac function assessment, though SMA generally does not affect the myocardium, it is imperative to remain vigilant about the potential development of pulmonary hypertension and even right heart failure in patients with severe deformities due to prolonged hypoxemia. Routine preoperative electrocardiograms and echocardiograms should be performed.

(4) Other aspects.
SMA patients frequently encounter a variety of nutritional challenges. [91] Some individuals face developmental and dietary issues due to restricted mouth opening, difficulties in eating, or swallowing problems. In contrast, others may manage to eat satisfactorily but become obese owing to diminished muscle strength and decreased physical activity. Irrespective of their specific nutritional concerns, it is crucial to actively address these issues before surgical procedures to make them better withstand the anesthesia. Additionally, SMA patients often experience multiple joint contractures, potentially complicating their positioning during surgical operations, which requires careful preparation.

Recommendation: SMA patients should undergo thorough and systematic evaluation before scoliosis correction surgery due to their complex underlying conditions (Grade II recommendation, Level C evidence).

6.6.2.2. Intraoperative management

(1) Anesthesia method.
Scoliosis correction surgery usually employs general anesthesia and routine spinal nerve electrophysiological monitoring during the operation. Since inhaled anesthetics and muscle relaxants may affect the accuracy of electrophysiological monitoring, total intravenous anesthesia and non-depolarizing muscle relaxants are recommended to complete anesthesia induction. Muscle relaxants are usually not added during the operation.

(2) Airway management.
SMA scoliosis correction surgery is usually performed using a posterior approach with conventional single-lumen endotracheal intubation. An anesthesiologist with experience in dealing with difficult airways should be arranged with appropriate airway tools for patients with difficult airways. Awake bronchoscopic intubation should be performed when necessary. Controlled ventilation is usually used during surgery with protective lung ventilation strategies. [92] A complete extubation strategy should be formulated before removing the endotracheal tube from patients with difficult airways after surgery, including a plan for re-intubation when necessary.

(3) Intraoperative monitoring.
① Routine monitoring. During surgery, an electrocardiogram, non-invasive blood pressure, pulse oximetry, and end-tidal carbon dioxide monitoring should be performed. It is also recommended to monitor the depth of anesthesia to avoid awareness or excessive anesthesia during surgery. It can also help estimate the appropriate time for awakening patients scheduled for intraoperative arousal. ② Circulatory monitoring. Since SMA scoliosis correction surgery is expected to be traumatic with a long duration and significant bleeding, invasive arterial blood pressure monitoring is essential. [93] In addition to real-time blood pressure monitoring, various derivative indicators based on invasive arterial pressure waveforms can be used to guide volume management. Furthermore, arterial catheterization is valuable for blood gas analysis and the dynamic assessment of the patient's internal environment, thereby aiding in the adjustment of mechanical ventilation settings. [94] Due to the challenges in establishing large-bore peripheral venous access in SMA patients, central catheterization becomes necessary when needed due to muscle atrophy and poor peripheral venous conditions. [89] ③ Body temperature monitoring. The lengthy and traumatic nature of scoliosis correction surgery, coupled with a high risk of hypothermia, necessitates proactive body temperature monitoring and management. [95] Utilizing nasopharyngeal temperature probes and urinary catheters with a temperature sensor allows for accurate monitoring of the patient's core temperature. The patient's core temperature can be maintained at no less than 36 °C by warming infusions and blood transfusions, using warming blankets, warming flushing fluids, and adjusting the room temperature.

(4) Circulation and blood transfusion management.
As mentioned above, scoliosis correction surgery in SMA patients is expected to cause significant trauma and heavy bleeding, so perioperative

management should be emphasized. Research indicates that addressing preoperative anemia, employing antifibrinolytic agents like tranexamic acid, appropriate antihypertensive treatment, utilizing intraoperative autologous blood recovery techniques, and adhering strictly to transfusion criteria can significantly lower both intraoperative and postoperative blood loss, and reduce the rate of allogeneic blood transfusion. [96-97]

For SMA patients with scoliosis who have compromised growth, nutritional status, and low body weight, managing perioperative volume is particularly challenging. Goal-directed fluid therapy can be applied and adjusted in real-time based on objective indicators like stroke volume variability, pulse pressure variability, and the patient's response to the fluid infusion.

In addition, spinal surgery in the prone position can have a significant impact on circulation and ventilation, requiring special attention. During the operation, the compression of the chest and the inferior vena cava can lead to apparent circulatory fluctuations, which should be promptly handled or communicated with the surgeon. If necessary, the operation should be suspended until the circulation is stable.

Recommendation: The scoliosis correction surgery can be extensive, with significant trauma and considerable bleeding. Therefore, it is crucial to enhance intraoperative monitoring to promptly address patient condition changes (Grade II recommendation, Level C evidence).

6.6.2.3. Postoperative management

(1) Postoperative care.
A comprehensive assessment should be conducted based on the patient's preoperative condition, the extent of the surgery, the magnitude of the trauma, intraoperative blood loss, circulation, and respiratory function. For SMA, patients with poor preoperative pulmonary function and muscle strength should be returned to the intensive care unit for further treatment if necessary. After surgery, it's recommended to closely monitor the patient's drainage volume, hemoglobin level, and coagulation function to detect postoperative bleeding. Blood transfusion can be given when necessary. Blood pressure and heart rate should continue to be monitored. Patients should be encouraged to cough, expectorate, and strengthen breathing exercises to prevent atelectasis and lung infection.

(2) Postoperative analgesia.
Scoliosis correction surgery is very traumatic, and most SMA patients who undergo this surgery are adolescents with high postoperative pain levels. Good analgesia helps patients recover and ensures their quality of life and mental health. It is essential to do excellent perioperative pain management. Multimodal analgesia technology can better manage postoperative pain. [98-99] Opioids are still the central analgesics after scoliosis correction surgery, but they are often accompanied by adverse reactions such as nausea, vomiting, itching, and constipation. [100] Regional anesthesia technology and local wound infiltration anesthesia are safe and effective auxiliary means to relieve postoperative pain. They can reduce the use of opioids, lower postoperative pain scores, and promote early postoperative recovery of patients. [101]

Recommendation: SMA patients have high postoperative pain levels after spinal correction surgery. Multimodal analgesia technology is recommended to accelerate postoperative recovery (Grade II recommendation, Grade B evidence).

(This part was written by Weiyun Chen.)

6.7. Orthopedic management

Muscle weakness in SMA patients can lead to a variety of musculoskeletal deformities. Trunk muscle weakness often leads to spinal deformities characterized by scoliosis and kyphosis, with the prevalence of scoliosis at about 60%. [102] Intercostal muscle weakness can cause typical parasol rib deformity and bell-shaped chest. [103] Kyphosis further aggravates chest deformity and pulmonary dysfunction. Most scoliosis singly involves the thoracolumbar segment. [104] As the kyphosis progresses, patients may experience sitting imbalance. Long-term seated on a single buttock can lead to hip dysplasia, hip subluxation, and even dislocation on the non-weight-bearing side. The weight-bearing side of the pelvis can have hemipelvic dysplasia due to long-term abnormal weight-bearing. Compensatory cervicothoracic scoliosis aggravates head control disorders and swallowing disorders. Long-term reduced activity or improper care can lead to large

joints such as the hip, knee, ankle, elbow, and wrist contractures.

6.7.1. Treatment of Scoliosis

6.7.1.1. Bracing

Scoliosis is a critical aspect in the orthopedic management of SMA patients, which is often early-onset and progressive even after bone maturity. When the main curve's Cobb angle is below 20°, vigilant monitoring is typically advised. In cases where the main curve's Cobb angle exceeds 20° and the bones have not yet matured, it is recommended to obtain anterior and lateral X-rays of the full spine every six months to observe the progression. When the Cobb angle surpasses 20° or the maximum kyphosis angle exceeds 50°, the brace is considered. [105] Despite numerous studies indicating that brace treatment does not halt the progression of scoliosis in SMA patients and may even limit thoracic development and exacerbate pulmonary dysfunction, [106] it remains valuable for maintaining sitting posture. Therefore, brace treatment continues to be utilized in managing scoliosis in SMA patients.

Recommendation: SMA patients with Cobb angles exceeding 20° or maximum kyphosis angles exceeding 50° can be treated with bracing (Grade III recommendation, Level D evidence).

6.7.1.2. Non-fusion spinal surgery

Spinal correction surgery is recommended for scoliosis with a Cobb angle greater than 50°. A study has shown that the progression of scoliosis in SMA patients before spinal correction surgery can exceed 10 degrees per year. [107] When considering surgery for spinal deformity, it's crucial to also take into account the associated trunk imbalance and low back pain, the sitting imbalance due to pelvic tilt, and the potential for progressively worsening lung function resulting from thoracic deformity.

Before scoliosis correction surgery, a multidisciplinary evaluation is required by the orthopedics, endocrinology, respiratory, anesthesia, and nutrition departments. Most patients cannot stand and walk before surgery, so standard erect anterior and lateral X-rays of the entire spine may be difficult to complete. Since correcting pelvic tilt and maintaining sitting posture are essential goals of scoliosis surgery, it is recommended to perform sitting anterior and lateral X-rays of the entire spine before surgery to assess the severity of scoliosis and pelvic tilt. Bone loss is common in SMA patients. [108] 38% of patients have experienced fragility fractures, although only 13% of patients meet the diagnostic criteria for osteoporosis, with the femur being the most common fracture site. [109] Intravenous bisphosphonates can effectively reduce the fracture rate in SMA patients. [110] Therefore, for SMA patients with osteoporosis, intravenous bisphosphonates can be used before surgery to improve bone density and reduce complications related to internal fixation. Preoperative pulmonary function tests and blood gas analysis are recommended for preoperative evaluation. For patients with severe rigid scoliosis accompanied by pulmonary dysfunction or respiratory failure, applying preoperative halo-gravity traction is highly beneficial. This method enhances spinal flexibility, easing the complexity of surgical correction, and significantly improves pulmonary function and nutritional status, amplifying the safety of both anesthesia and the surgical procedure.

For SMA patients with early-onset scoliosis, less than eight years, non-fusion surgery that preserves growth potential is recommended. Traditional growing rods, vertically extendable prosthetic titanium ribs, and magnetically controlled growing rods have been reported to effectively improve early-onset scoliosis in SMA patients. [111-113] Unlike traditional growing rods, magnetically controlled growing rods and vertically extendable prosthetic titanium ribs can lengthen the spine without repeated anesthesia or surgery. [114]

Recommendation: Non-fusion surgery is feasible for SMA patients under eight years old with a Cobb angle exceeding 50° (Grade III recommendation, Level D evidence).

6.7.1.3. Spinal Fusion Surgery

For patients over 12 years old with nearly or fully matured skeletal structures, spinal fusion surgery is typically advised. In the case of children aged 8 to 12 years, the decision between fusion and non-fusion surgical approaches largely hinges on the level of skeletal maturity and potential for spinal growth. The current standard procedure for spinal fusion surgery in patients with SMA involves the use of posterior pedicle screw fixation. For those patients whose pelvic tilt significantly impacts sitting balance, spinal pelvic fixation is recommended. The implantation of sacral-2-alar-iliac (S2AI) screws

has emerged as a viable method for pelvic fixation in SMA patients, effectively correcting pelvic tilt. Pelvic CT scans and 3D printing technology are advised to assess pelvic development thoroughly before surgery. For practitioners with limited experience in manual screw placement, the incorporation of an intraoperative O-arm machine and navigation technologies can enhance the precision of S2AI screw placement. In managing severe scoliosis, employing a multi-rod fixation approach that focuses on "local correction and overall balance" is beneficial.

Recommendation: Spinal fusion surgery can be performed for SMA patients over 12 years old with a Cobb angle exceeding 50° (Grade III recommendation, Level D evidence).

6.7.1.4. Intraoperative lamina fenestration

Currently, gene modification therapies are being employed in treating SMA due to their ability to significantly improve pulmonary function, motor function, and the natural history of patients. Among them, nusinersen requires intrathecal injection. Lamina fenestration on the convex side of the lumbar 3/4 segment, approximately 15 mm by 20 mm in size, allows for postoperative intrathecal injection for patients with severe spinal deformities who are unable or find it challenging to administer the drug. For those already on a regular regimen of nusinersen injections, undergoing spinal fusion surgery during the maintenance phase of their treatment is recommended. The first intrathecal injection after surgery should be scheduled for three months later, requires assessment of incision healing, and rule out infection by checking blood routine, ESR, and CRP.

Recommendation: During spinal correction surgery for SMA patients, lamina fenestration can be done to reserve a channel for postoperative nusinersen intrathecal injection (level IV recommendation, level D evidence).

6.7.2. Treatment of other musculoskeletal deformities

Non-fusion devices combined with lateral chest wall support can improve chest collapse in SMA patients, but may have no positive effect on lung function. [113] Research on hip pain in SMA patients is still controversial. Previous reports have shown that SMA patients rarely experience hip pain, and based on this, it is believed that patients with hip instability do not need surgical treatment. [115-116] Recent studies have shown that more than half of SMA patients experience hip pain, and about 14% of patients experience moderate to severe hip pain. Independent risk factors for hip pain include obesity, hip contracture, hip dislocation, and spinal orthopedic surgery. [117] Among them, hip pain is more common in patients with type 2 SMA. When hip pain seriously affects daily life, such as sitting and lying, surgical treatment can be considered. Simple hip open reduction surgery is not ideal and has a high risk of re-dislocation after surgery. [118] Moreover, even if the reduction is maintained, it cannot improve patient satisfaction. [116] Joint contractures are common in SMA patients. [119] For patients with large joint contractures affecting joint function and daily life, arthrolysis can be performed. However, recent studies have shown that although surgical intervention can relieve hip pain in most patients, only a very small number of patients can completely control pain. [120]

Recommendation: For SMA patients with large joint contractures affecting joint function and daily life, arthrolysis can be performed (Grade IV recommendation, Grade D evidence).

(This part was written by Jianxiong Shen)

Author Contributions

The corresponding authors (Yi Dai and Liying Cui) were responsible for planning the entire guideline, forming the expert team, and promoting the formulation of the guideline. The leading writers of the 12 specialty sections are marked after each section. All experts participated in the discussion of the corresponding part of the guideline, put forward many revisions, and improved the guideline. Finally, the final draft, approved by all experts, was submitted for publication.

Conflict of interests

None.

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List of abbreviations

SMA spinal muscular atrophy; SMN1 survival motor neuron 1; OMIM Online Mendelian Inheritance in Man; EMG electromyography; CK creatine kinase; CAMP compound muscle action potential; MLPA multiplex ligation-dependent probe amplification; PCR Polymerase Chain Reaction; MRI magnetic resonance imaging; cerebrospinal fluid CSF; DMT disease modifying treatment; HFMSE Hammersmith Functional Motor Scale Expand; RULM Revised Upper Limb Module; HINE-2 Hammersmith Neurological Examination Section 2; CHOP-INTEND Children's Hospital of Philadelphia infant test of neuromuscular disorders; SMD standardized mean difference; ESE2 exonic splicing enhancer 2; MFM32 Motor Function Measure 32; AAV9 adeno-associated virus type 9; MDT multidisciplinary team; ALSFRS Amyotrophic Lateral Sclerosis Functional Rating Scale; MUNE motor unit number estimation; MCV motor conduction velocity; MUNIX Motor Unit Number Index; DXEA Dual Energy X-ray Absorptiometry; 3D three-dimensional; FVC forced vital capacity; FEV1 forced expiratory volume in the first second; PEF peak expiratory flow; FOV field of view; T1 WI T1 Weighted Imaging; STIR Short-Time Inversion Recovery; FF fat fraction; PHQ-9 Patient Health Questionnaire-9; GAD-7 Generalized Anxiety Disorder-7; SAS self-rating anxiety scale; SDS self-rating depression scale; SCL-90 symptom check list 90; ICF International Classification of Functioning, Disability, and Health; GMFM Gross Motor Function Measure; CHOP-ATEND Children's Hospital of Philadelphia Adult Test of Neuromuscular disorders; TUGT Timed Up and Go test; 6MWT 6-Minute Walk Test; ATS American Thoracic Society; ROM range of motion; SMAFRS Spinal Muscular Atrophy Functional Rating Scale; SF-36 36-Item Short Form Survey; HRQoL health-related quality of life; PF physical functioning; RP), role-physical; BP bodily pain; SF social functioning; MH mental health; RE role-emotional; VT role-emotional; GH general health; PEmax maximum expiratory pressure; PImax maximum peak inspiratory pressure; PCF peak cough flow; REM rapid eye movement; CSA central sleep apnea; OSA obstructive sleep apnea; PSG polysomnography; BPAP bilevel positive airway pressure; 25-OHD 25-hydroxyvitamin D levels; PINP procollagen type 1 N-terminal propeptide; CTX carboxy-terminal cross-inked telopeptide of type 1 collagen; DXA dual-energy X-ray absorptiometry; rhPTH1-34 recombinant human parathyroid hormone 1-34; IGF-1 Insulin-like growth factor 1; HOMA-IR homeostatic model assessment of insulin resistance; OGTT oral glucose tolerance test; GER Gastroesophageal reflux; GLIM Global Leadership Initiative on Malnutrition; NRS2002 Nutritional Risk Screening 2002; MNA-SF mini nutritional assessment-short form; MUST malnutrition universal screening tool; BMI body mass

index; STAMP screening tool for assessing malnutrition in pediatrics; HHD handheld dynamometry; ONS oral nutritional supplements; EN enteral nutrition; ESPGHAN European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; VAS visual analogue scale; FOIS functional oral intake scale; ASO antisense oligonucleotide; CDE Center for Drug Evaluation; LP lumbar puncture; VG vectorgenomes; FSTAs fast skeletal muscle troponin activators. ♦

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