World Journal of Pediatrics (2024) 20:983–1002
https://doi.org/10.1007/s12519-024-00819-w

REVIEW ARTICLE

Guidelines for the diagnosis and treatment of neurally mediated syncope in children and adolescents (revised 2024)

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Received: 18 April 2024 / Accepted: 17 May 2024 / Published online: 7 August 2024
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Abstract

Background Significant progress has been made in the diagnosis and treatment of pediatric syncope since the publication of the "2018 Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents" ("2018 Edition Guidelines"). Therefore, we have revised and updated it to assist pediatricians in effectively managing children with syncope.

Data sources According to the "2018 Edition Guidelines", the expert groups collected clinical evidence, evaluated preliminary recommendations, and then organized open-ended discussions to form the recommendations. This guideline was developed by reviewing the literature and studies in databases including PubMed, Cochrane, EMBASE, China Biomedical Database, and Chinese Journal Full-text Database up to April 2024. Search terms included "syncope", "children", "adolescents", "diagnosis", and "treatment."

Results The guidelines were based on the latest global research progress and were evidence-based. The classification of syncope etiology, diagnostic procedures, postural tests, such as the active standing test, head-up tilt test, and active sitting test, clinical diagnosis, and individualized treatment for neurally mediated syncope in pediatric population were included.

Conclusions The guidelines were updated based on the latest literature. The concepts of sitting tachycardia syndrome and sitting hypertension were introduced and the comorbidities of neurally mediated syncope were emphasized. Some biomarkers used for individualized treatment were underlined. Specific suggestions were put forward for non-pharmacological therapies as well as the follow-up process. The new guidelines will provide comprehensive guidance and reference for the diagnosis and treatment of neurally mediated syncope in children and adolescents.

Keywords Adolescents · Children · Diagnosis · Neurally mediated syncope · Treatment

Introduction

Syncope is a transient loss of consciousness (TLOC) and inability to maintain the posture caused by transient global cerebral hypoperfusion. It is characterized by a rapid onset, short duration, and spontaneous complete recovery [1–4] (I; C). Syncope, a common disorder in children and adolescents, has an incidence of 17.37% [5], with a higher occurrence in girls than in boys [6] (IIa; B). It accounts for 1%–2% of visits to the emergency department [1]. The pathogenesis, etiology, diagnosis, and treatment of pediatric syncope differ from those in adults. Recurrent syncope can seriously impact the physical and mental health, learning abilities, and quality of life of

The members of the group Chinese Pediatric Cardiology Society, Chinese Pediatric Society, Chinese Medical Association; Committee of Pediatric Syncope, College of Pediatricians, Chinese Medical Doctor Association; Pediatric Cardiology Society, Beijing Pediatric Society, Beijing Medical Association; Committee of Pediatric Cardiology, College of Cardiovascular Physicians, Chinese Medical Doctor Association are listed in Acknowledgements.

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affected children [7, 8] (IIa; A). In some cases, syncope with cardiogenic causes can even pose a risk of sudden death. From 2015 to 2018, the Heart Rhythm Society, the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, the Canadian Cardiovascular Society, the Canadian Pediatric Cardiology Association, and the European Society of Cardiology successively published guidelines or society position statements on the diagnosis and management of syncope and related syndromes [2, 9–11] (I; C). In 2018, professional societies including the Chinese Pediatric Cardiology Society, Chinese Pediatric Society, Chinese Medical Association; Committee of Pediatric Syncope, College of Pediatricians, Chinese Medical Doctor Association; Pediatric Cardiology Society, Beijing Pediatric Society, Beijing Medical Association; Committee of Pediatric Cardiology, College of Cardiovascular Physicians, Chinese Medical Doctor Association released the "2018 Chinese Pediatric Cardiology Society (CPCS) guidelines for diagnosis and treatment of syncope in children and adolescents" (hereafter referred to as the "2018 Edition Guidelines") [1] to promote the standardized diagnosis and treatment of syncope in children and adolescents. In recent years, significant progress has been made in the clinical diagnosis and treatment of syncope, especially neurally mediated syncope (NMS) in children and adolescents, including the etiological classification of syncope, diagnostic procedures, posture tests, such as the active standing test, the head-up tilt test (HUTT), as well as the active sitting test, clinical diagnosis, and individualized treatment [12–25]. The “Guidelines for the diagnosis and treatment of neurally-mediated syncope in children and adolescents (revised 2024)” were developed based on the "2018 Edition Guidelines" and followed the latest global research advances. However, more large-scale, multi-center, randomized controlled clinical studies are needed to provide a higher level of evidence for the treatment of NMS in children and adolescents [26].

Classes of recommendations and levels of evidence to manage pediatric syncope

The classes of recommendations and levels of evidence for the management of pediatric syncope were weighed and graded based on predefined scales (Tables 1, 2) [1, 2] (I; C).

The underlying diseases of syncope in children and adolescents

The causes of syncope in children and adolescents include NMS, cardiac syncope (CS), and unexplained syncope (UPS) [1]. NMS is the most common cause accounting for 70%–80%, CS accounts for 2%–3%, and UPS accounts for about 20% [7] (I; C). The causes of syncope in children and adolescents are classified and listed in Table 3.

NMS in children and adolescents is characterized by syncopal attacks caused by abnormal reflex regulation or dysfunction of the autonomic nervous system, mainly referring to vasovagal syncope (VVS) and postural orthostatic tachycardia syndrome (POTS), which accounts for about 95% of NMS [4, 27–30] (IIa; B). Breath-holding spells in infancy may be a specific type

Table 1 Classes of recommendations for the management of pediatric syncope

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that the given treatment or procedure is beneficial, useful and effective	Is recommended/indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion favors the usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful	Is not recommended

Table 2 Levels of evidence for the management of pediatric syncope

Level of evidence	Source of evidence
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of opinion of experts and/or small studies, retrospective studies, registries

Table 3 Classification of syncope in children and adolescents

Classes	Underlying diseases and associated syndrome
Neurally mediated syncope	Vasovagal syncope Vasoinhibitory type Cardioinhibitory type Mixed type Postural orthostatic tachycardia syndrome Orthostatic hypotension Orthostatic hypertension Sitting tachycardia syndrome Sitting hypertension Situational syncope Carotid sinus syndrome
Cardiac syncope	Arrhythmia Structural cardiac diseases, including cardiomyopathy, etc.
Unexplained syncope	

of NMS [31, 32] (I; C). In children and adolescents, NMS is often associated with comorbidities [33, 34]. Nearly 30%–40% of children and adolescents with VVS and/or POTS generally also have allergic diseases [35] (IIa; B), and some may also be associated with coagulation disorders [36], but patent foramen ovale may not increase the risk of pediatric syncope [37] (IIa; B). Other common comorbidities include migraines, mental disorders, sleeping disorders, hyperventilation syndrome, chronic fatigue syndrome, joint hypermobility syndrome, and gastrointestinal disorders. Comorbidities may increase the complexity of diagnosis and treatment [38] (IIa; B).

CS is mainly caused by abnormal structure or rhythm of the heart. Although CS is a relatively rare cause of pediatric syncope, it is associated with a high risk of sudden death and needs to be diagnosed as early as possible [39] (IIa; B).

Other causes of TLOC [7, 40] (IIa; A), including epileptic seizures, metabolic disorders (e.g., hypoglycemia and hypoxemia), poisoning, and psychological pseudosyncope (PPS) [41–43] (IIa; B), can sometimes be misdiagnosed as syncope. These disorders do not produce transient cerebral hypoperfusion, and thus, should be strictly differentiated from syncope.

Diagnosis

Diagnostic procedures for pediatric syncope

As shown in Fig. 1, the diagnostic procedures comprise three steps [44] (IIa; B). In the first step, after medical history taking, physical examination, supine and upright blood pressure (BP) measurement, and supine and upright electrocardiogram (ECG) recording, the patients can be divided into three groups: definite diagnosis, suggestive diagnosis, and UPS [1].

Definitive diagnosis

POTS, orthostatic hypotension (OH), orthostatic hypertension (OHT) [45, 46] (IIa; A), sitting tachycardia syndrome (STS), and sitting hypertension (SHT) [47, 48] (IIa; B) can be indicated by the history of symptoms of orthostatic intolerance (OI) or sitting intolerance. A diagnosis can be confirmed when patients with typical symptoms have a normal ECG and a positive result in an active standing test, HUTT, or active sitting test [49–56] (IIa; B). Situational syncope (SS) is defined as syncope in specific situations, such as micturition, defecation, bathing, swallowing, cough, post-dinner, singing, teeth brushing, and hair grooming [57, 58] (IIa; B). Drug-induced syncope (determined through medication history) can be diagnosed by typical history.

Suggestive diagnosis

The patients with suggestive diagnosis after the first step, as seen in Fig. 1, need further laboratory investigations in step 2. In step 2, cardiomyopathy, pulmonary hypertension, cyanotic congenital heart disease, and some types of arrhythmias can be suspected according to the clues from history, physical examination, and ECG findings. For example, onset in infancy or early childhood, exercise-induced events [59] (IIa; B), family history of genetic heart disease or sudden death, and abnormal ECG findings can suggest CS, with the strongest clues provided by exercise-induced syncope and abnormal ECG findings [60, 61]. For such patients, further examinations are needed to ensure the diagnosis, such as repetitive ECG, Holter ECG, implanted loop recorder (ILR) [62] (IIa; B), exercise test, intracardial electrophysiology, angiography, cardiovascular imaging, screening of metabolic disorder or genetic tests, based on the specific situation [46, 63] (IIa; B).

Unexplained diagnosis

In step 3, for patients whose diagnosis cannot be confirmed or indicated by detailed medical history, physical examination, supine BP, and ECG measurements [48] (IIa; A), if the symptoms occur more than once and the characteristics of the attacks suggest NMS, postural tests such as the active standing test, HUTT [9, 64–66] (IIa; B), and active sitting test [47, 48] (IIa; A) can be performed. These tests may help in diagnosing NMS and determining its hemodynamic type.

If a definite diagnosis cannot be achieved even after the above steps are taken, a re-evaluation is needed. This includes history-retaking, physical re-examination, and further laboratory examinations. Moreover, assessment by associated specialists such as neurologists or psychiatrists should be considered when necessary.

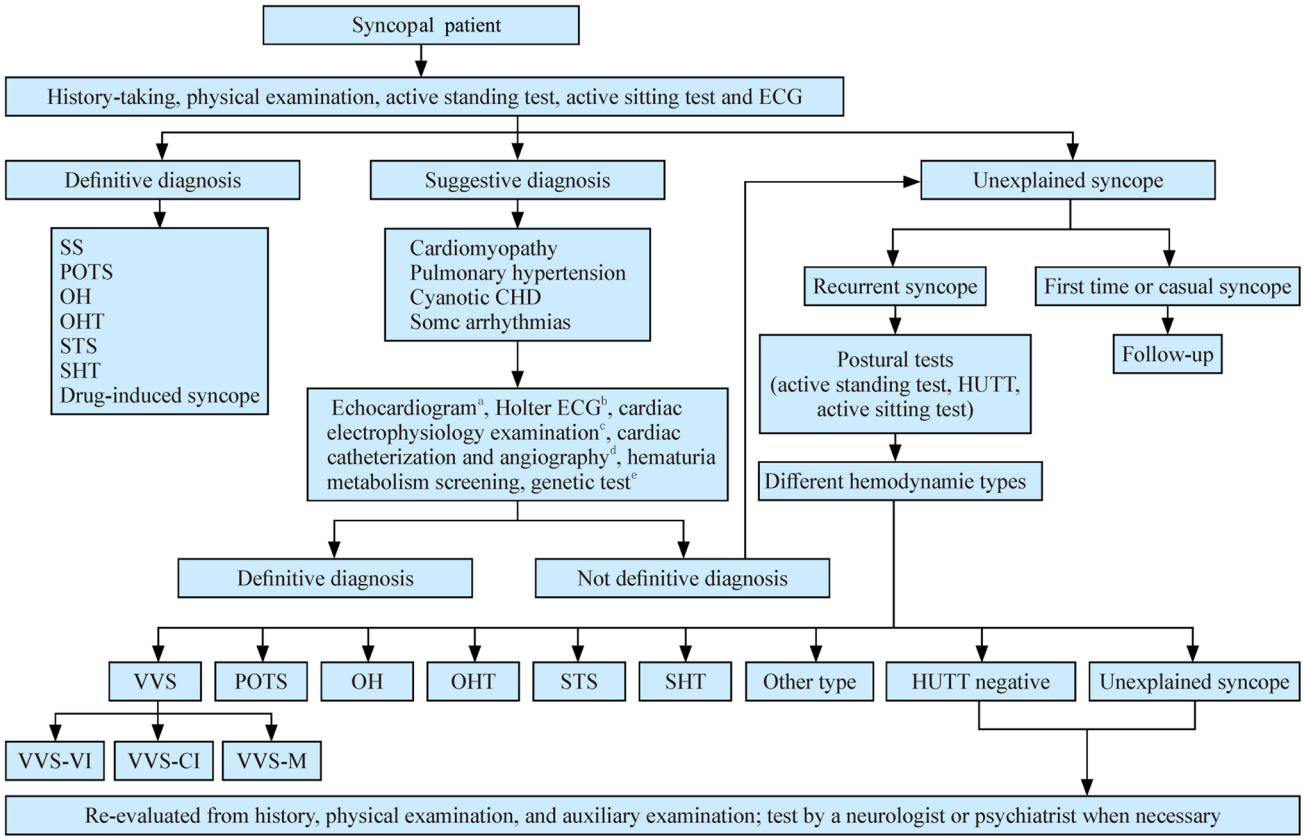

Fig. 1 Diagnostic procedure for pediatric syncope. *ECG* electrocardiogram, *SS* situational syncope, *POTS* postural orthostatic tachycardia syndrome, *OH* orthostatic hypotension, *OHT* orthostatic hypertension, *STS* sitting tachycardia syndrome, *SHT* sitting hypertension, *CHD* congenital heart disease, *HUTT* head-up tilt test, *VVS* vasovagal syncope, *VVS-VI* vasovagal syncope vasoinhibitory type, *VVS-CI* vasovagal syncope cardioinhibitory type, *VVS-M* vasovagal syncope mixed type. [a]For children with normal physical examination and normal routine ECG findings, ECG is generally not helpful in determining possible reasons. For children with possible structural heart defects after medical history, physical examination, and routine ECG. ECG is a screening tool to detect abnormal cardiac structures or functions; [b]Holter ECG is a common test to determine the cause of syncope. However, because syncope is unpredictable, regular monitoring for only 24 hours makes it difficult to confirm or thoroughly rule out the association between arrhythmia and syncope. When diagnosing the cause of syncope, comprehensive judgment should be made together with history-taking and other tests. The possible reasons include asymptomatic sinus bradycardia, atrioventricular block, and endless supraventricular or ventricular tachycardia. For children with recurrent syncope, Holter ECG and ILR are important for diagnosis and differential diagnosis. For children with syncope induced by sports and emotions, an exercise test should be performed to detect potential arrhythmias. During exercise trials, first aid is prepared as a precaution; [c]for patients with suspected sick sinus syndrome, atrioventricular conduction abnormalities, and/or all ventricular and supraventricular arrhythmias, the diagnosis can be confirmed by cardiac electrophysiological examination when necessary; [d]for patients with suspected pulmonary hypertension or coronary heart disease, although ECG cannot clarify the diagnosis, cardiac catheterization and angiocardiography may be considered; [e]for patients with suspected hereditary disease, such as ion channel diseases, cardiomyopathy, or genetic metabolic diseases, and for those with a family history of genetic heart disease or sudden death, the diagnosis may be confirmed by metabolic disorder screening and/or genetic tests

Methodology of postural tests

Active standing test

The active standing test can be performed to screen for underlying causes of OI in children. It has no absolute contraindications.

The protocol First, the children are asked to lay supine for 10–30 minutes to obtain supine heart rate (HR), BP, and ECG recordings. Then, the children are told to actively stand for another 10 minutes, simultaneously monitoring the above parameters [65–67] (IIa; A).

Clinical comments During the active standing test, the children should be closely observed to determine whether they have presyncope symptoms or even syncope, and the test can help diagnose POTS [66, 67], OH [66, 68], or OHT [66, 69] (IIa; B). Here, the presyncope consists of symptoms including dizziness, headache, chest tightness, palpitations,

nausea, vomiting, pallor, cold sweats, blurred vision, hearing loss, abdominal pain, and variable degrees of altered consciousness without complete loss of consciousness. HR, BP, and ECG are monitored in the supine position. When the ECG electrode does not move, observations of OI, HR, BP, and ECG are made for 10 minutes after assuming an upright position. Changes in HR and ECG waveforms between supine and upright positions are compared. Significant changes in T-wave morphology of decubitus and upright ECG help judge autonomic nervous function [70, 71] (IIa; B). In patients with clinical manifestations of OI but with a negative active standing test result, the HUTT could be considered if they do not have contraindications. Criteria for the positive response for POTS, OH and OHT refer to relevant section of "Criteria for the positive response of active standing test and head-up tilt test".

Head-up tilt test

Indications and contraindications Indications for the HUTT include (1) to clinically confirm a suspected NMS, which cannot be diagnosed by other tests [1, 72] (I; C) and (2) to make a differential diagnosis with pseudosyncope [42, 73] (IIa; B). Contraindications for the HUTT are (1) known aortic stenosis or left ventricular outflow tract obstruction; (2) severe mitral stenosis; (3) definite pulmonary hypertension or right ventricular outflow tract obstruction; (4) serious stenosis in the proximal coronary artery; (5) definite severe cerebrovascular diseases; and (6) syncope caused by definite arrhythmia [1] (I; C).

Preparation for the head-up tilt test The test environment must be quiet with dim light, a comfortable room temperature, and no distractions [1] (I; C). Medicines such as nitroglycerin tablets for sublingual nitroglycerin-provoked HUTT, adrenaline, atropine, and first aid equipment, including an oxygen inhalation device and defibrillator, should be prepared.

The tilt table should have supported foot pedals, with fences on both sides and fixed belts for the chest and knee joints to avoid knee flexion and falling. The electric table board should be well-controlled and move smoothly so that the table can be tilted to a certain angle from the horizontal position and return to a horizontal position from any tilted angle [74] (IIa; B).

The operators should cautiously observe the details of the patient's manifestations suggesting syncope or presyncope attacks and must be familiar with the rules to stop the test and rescue program of the HUTT [75] (I; C). The detailed procedure of the HUTT should be explained to children and their legal guardians/parents to relieve their anxiety and obtain their cooperation during the whole test [1] (I; C).

Informed consent: the HUTT has certain potential risks, such as a fainting attack or significant hemodynamic changes such as cardiac asystole [76–80] (IIa; B). Therefore, detailed instructions and risks should be described to children and their legal guardians/parents, and signed informed consent should be obtained before the test [81] (IIa; B).

Preparation of the pediatric patient: any vasoactive drugs should be discontinued for at least five half-lives. Food and beverages, such as coffee, that might affect autonomic nervous system functions should be avoided for at least 24 hours before the test. Children should fast for at least 4 hours before the test. The test should be performed in the morning [67, 82] (IIa; B) without the presence of unrelated persons [72].

Steps of the head-up tilt test Basic HUTT (BHUT): children should first lie on the tilt bed in a horizontal position for around 10–30 minutes with fixed bands to avoid buckling of knee joints. HR, BP, and ECG recordings are taken during this period. Then, the bed is tilted upward at an angle of 60° and HR, BP, and ECG are simultaneously monitored. The test must be stopped, and the children should be placed in the supine position (from the upright position) when the children show a positive response (see section "Criteria for the positive response") or have completed the whole 45 minutes process, or if the patient requires stopping for any reason [83, 84] (IIa; B).

Sublingual nitroglycerin-provoked HUTT (SNHUT): if no positive response has been developed during the BHUT, the children are suggested to undergo a SNHUT, in the same position for a further 20 minutes after sublingual administration of nitroglycerin at a dose of 4–6 μg/kg (maximum ≤ 300 μg) [85] (IIa; B). The endpoint of the test is a positive response or completion of the process. After the administration of the medicine as mentioned above, HR, BP, ECG, and clinical performance should be carefully recorded simultaneously [86, 87] (IIa; A).

Criteria for the positive response of active standing test and head-up tilt test Vasovagal syncope: syncopal episodes or presyncope symptoms together with any of the following responses in the HUTT are considered positive responses: (1) systolic BP (SBP) ≤ 80 mmHg (1 mmHg = 0.133 kPa) or diastolic BP (DBP) ≤ 50 mmHg, or mean pressure decrease ≥ 25%; (2) HR < 75 bpm for children aged 4 to 6 years, < 65 bpm for children aged > 6 to 8 years, and < 60 bpm for children and adolescents > 8 years; (3) ECG showing sinus arrest or junctional escape rhythm; (4) atrioventricular block (II or III degree) or cardiac arrest ≥ 3 seconds. The responses are classified as VVS vasoinhibitory type (VVS-VI), VVS cardioinhibitory type (VVS-CI), or VVS mixed type (VVS-M). VVS-VI is characterized by a significant decrease in BP without an obvious decrease in

HR, VVS-CI by a marked decrease in HR without a marked decrease in BP, and VVS-M by both an HR and BP decrease [1, 45, 88, 89] (IIa; A). Malignant VVS is characterized by cardiac arrest lasting more than 3 seconds during a syncope episode or the test [90, 91] (IIa; B).

Postural orthostatic tachycardia syndrome: the diagnosis of POTS is influenced by the circadian rhythm [92, 93] (IIa; B). It was reported that, during the active standing test for children, the difference in HR between supine and upright positions is more significant in the morning when compared with that in the afternoon or the evening [67] (IIa; B). Therefore, it is recommended to take a posture test in the morning (IIa; B). During the upright position of the active standing test or the initial 10 minutes of HUTT, a positive response for POTS is defined as a HR increase of ≥ 40 bpm or a maximum upright HR ≥ 130 bpm (in children aged 6 to 12 years old) or ≥ 125 bpm (in adolescents over 12 years older but under 18) [66, 87] (IIa; A). However, all positive responses should exclude significant BP decrease (where SBP decreases by > 20 mmHg and/or DBP decreases by > 10 mmHg).

Orthostatic hypotension: for classic OH, the supine BP is normal. During the initial 3 minutes of the active standing test or HUTT, SBP decreases at least by 20 mmHg and/or DBP decreases at least by 10 mmHg [1, 68] (I; C). The initial OH is defined by a transient BP decrease occurring within 15 seconds after standing.

Orthostatic hypertension: supine BP is normal and during the initial 3 minutes of the active standing test or HUTT, SBP increases by ≥ 20 mmHg and/or DBP increases by ≥ 25 mmHg (in children aged 6–12 years) or ≥ 20 mmHg (in adolescents aged 12–18 years) from supine to upright position; or upright BP is ≥ 130/90 mmHg (in children aged 6–12 years) or ≥ 140/90 mmHg (in adolescents aged 12–18 years) without an obvious change in HR [66, 94, 95] (IIa; B).

Characteristics of the head-up tilt test in children The autonomic nervous system of children is continuously developing and maturing, rendering it more unstable compared to that of adults. As a result, the hemodynamic parameters of the HUTT change more rapidly and abruptly, leading to positive responses appearing quite early in children. Additionally, children tend to cooperate less during the test than adults. Therefore, it is important to closely monitor and obtain the cooperation of children as much as possible during the HUTT. In most cases, children with POTS are more likely to demonstrate symptoms of OI than those with OH [96] (IIa; B). ECG changes such as sinus arrhythmia and sinus bradycardia in HUTT can predict an increased probability of positive responses [77] (IIa; B). Abnormal T-wave patterns, T-wave apex to T-wave end interval dispersion (Tped), and prolongation of the QT interval during the HUTT are useful in identifying children with VVS, who are more susceptible to ventricular arrhythmias with a latent risk of long QT syndrome [97] (IIa; B).

Safety issues of the head-up tilt test The HUTT should be performed following the indications and operation protocols to guarantee safety. The HUTT may induce syncope or presyncope symptoms leading to adverse events or complications such as arrhythmias [77], transient aphasia [78], convulsions [79], and fear [98] (IIa; B). However, the HUTT is generally considered safe when performed in accordance with the recommendations of the standard HUTT protocol and when syncope caused by organic heart diseases is fully excluded [72, 76, 81] (IIa; B). During the HUTT, long RR intervals > 2 seconds in ECGs are not rare. Returning the patient to the recumbent position in time can promote recovery in consciousness. For children aged 3–18 years, the HUTT demonstrates high specificity, and severe HUTT-related complications have been rarely reported in recent studies [76, 99, 100] (IIa; B).

Active sitting test

The operation is simple and relatively safe, serving as a preliminary screening tool to identify the basic etiology in children and adolescents presenting symptoms of sitting intolerance such as dizziness, blurred vision, headache, chest tightness, nausea, abdominal pain, numbness and sweating when sitting, without clear contraindications [47] (IIa; B).

The protocol After the children empty their bladder, the active sitting test is carried out in a quiet and comfortable room. The children are first asked to be in a supine position for 10 minutes and then in a sitting position for 10 minutes. Changes in HR and BP during sitting, as well as whether dizziness, pale face, fatigue, blurred vision, chest tightness, palpitations, abdominal pain, nausea, vomiting, and other symptoms of sitting intolerance occur during the test are dynamically observed and recorded. If the children are unable to complete the test, the test is terminated prematurely. STS and SHT can be diagnosed by an active sitting test [47, 101] (IIa; B).

Criteria for the positive response of active sitting test Sitting tachycardia syndrome: symptoms of sitting intolerance appear within 10 minutes after the change from a supine to a sitting position, and an increase in HR by ≥ 25 bpm after 3 minutes of sitting suggests STS [47, 102, 103] (IIa; B).

Sitting hypertension: symptoms of sitting intolerance occur within 10 minutes after the transition from a supine to a sitting position, and SBP elevation by ≥ 20 mmHg and/or DBP elevation by ≥ 20 mmHg within 3 minutes of sitting suggest SHT [47, 102, 103] (IIa; B).

Diagnostic criteria of neurally mediated syncope and associated syndromes

A detailed medical history can provide valuable information for diagnosis [60, 104] (IIa; A), and adherence to diagnostic guidelines may facilitate in correctly diagnosing patients experiencing syncope while avoiding unnecessary medical tests [39, 105–107]. Syncope is one of the common clinical manifestations of NMS in children and adolescents, although some cases can start with non-syncope symptoms, such as dizziness [108], tightness or pain in the chest [109], sigh or hyperventilation [110], palpitations [111], and abdominal pain [112, 113] (IIa; B).

Vasovagal syncope

The diagnostic criteria of VVS are as follows: (1) in most patients, it is associated with predisposing factors, such as persistent standing or sudden changes in body position (body position quickly changing to an upright position from supine or sitting or squatting), emotional stress, and crowded or stuffy environment; (2) a history of syncope is confirmed; (3) it features a positive hemodynamic response during a HUTT (see section "Criteria for the positive response of active standing test and head-up tilt test"); and (4) other causes of TLOC should be excluded [1, 114, 115] (IIa; B).

Postural orthostatic tachycardia syndrome

The diagnostic criteria of POTS are as follows: (1) the course of the disease is usually > 1 month and is often associated with most of the above-mentioned inducing factors (as seen in VVS). There are also some risk factors such as high basal HR in a supine position (a 10 bpm increase in HR in a supine position indicates an increased risk of POTS by 1.58 times), low water intake (water intake of children < 800 mL/day increases the risk of POTS by 3.88 times), insufficient sleep duration (i.e., children sleeping < 8 hours/day results in a 5.91 times increase in the risk of POTS) [116] (IIa; A); (2) OI symptoms include the main manifestations, such as dizziness, headache, fatigue, blurred vision, chest tightness, palpitations, hand tremors, intolerance to movement, and even syncope especially in an upright position [49, 117] (IIa; B); (3) a positive HUTT or active standing test result indicating POTS is required (see section "Criteria for the positive response of active standing test and head-up tilt test"); and (4) other diseases that may cause similar symptoms should be excluded [65] (IIa; A).

Orthostatic hypotension

The diagnostic criteria of OH are as follows: (1) it is often associated with most of the above-mentioned inducing factors (as seen in VVS); (2) OI often occurs immediately after standing; (3) a positive HUTT or active standing test result is required (see Section "Criteria for the positive response of active standing test and head-up tilt test"); and (4) other diseases that cause similar symptoms should be excluded [68].

Orthostatic hypertension

The diagnostic criteria of OHT are as follows: (1) it is associated with the above predisposing factors in most patients (as seen in VVS). Being overweight, defined as having a body mass index (BMI) above the 85th percentile for the same sex and age group, causes a 6.07 times increase in the risk of OHT, while obesity (BMI > 95th percentile) increases the risk of OHT by 7.48 times. Drinking less water (water intake < 800 mL/day) causes a 4.03 times increase in the risk of OHT. Increased sleep duration by 1 hour per night decreases the risk of OHT by 74.3% [118] (IIa; B); (2) it is often associated with OI during the upright position; (3) a positive HUTT or active standing test result is required (see section "Criteria for the positive response of active standing test and head-up tilt test"); and (4) other diseases that cause similar symptoms should be excluded [66, 94, 119] (IIa; B).

Sitting tachycardia syndrome

The diagnostic criteria of STS are as follows: (1) it involves precipitating factors such as a sudden change in position (from supine to sitting), mental tension, stuffy environment, and insufficient sleep duration in most patients [48] (IIa; A); (2) the patients have symptoms of sitting intolerance, and syncope can also occur in severe cases; (3) the change of HR reaches the criteria for the positive response of active sitting test (see section "Criteria for the positive response of active sitting test"); and (4) other diseases that cause similar symptoms should be excluded [47, 48] (IIa; A).

Sitting hypertension

The diagnostic criteria of SHT are as follows: (1) it involves many precipitating factors such as a sudden change in position (from supine to sitting), mental tension, stuffy environment, and insufficient sleep time in most patients; (2) the patients have symptoms of sitting intolerance, and syncope can also occur in severe cases; (3) the change of BP reaches the criteria for the positive response of active sitting test (see section "Criteria for the positive response of active sitting test"); and (4) other diseases that cause similar symptoms should be excluded [47, 48] (IIa; A).

Situational syncope

SS is a type of reflex syncope, presupposed by special situations and directly related to relatively fixed triggers. Most SS episodes occur in the upright position and nearly half of the patients have positive responses to HUTT. SS includes micturition syncope, defecation syncope, cough syncope, swallowing syncope, and breath-holding spells according to different induced situations [57, 58] (IIa; B).

Treatment

Vasovagal syncope

Significant progress has been made in the individualized treatment of VVS [4, 120–125], and a common strategy to prevent the onset of VVS is non-pharmacological treatment based on lifestyle changes [28, 126] (IIa; B).

Health education

After VVS is diagnosed, health education on the management of syncope, including basic knowledge and skills in self-protection, is required for patients and legal guardians/parents, which can help reduce episodes of syncope and the possible physical as well as psychological harm it causes to pediatric patients. A health education model using mind mapping can significantly improve the effectiveness of this education [127] (IIa; B).

Trigger avoidance: children with VVS and their legal guardians/parents are advised to recognize common triggers, such as prolonged standing, quick position changes from a prolonged supine or sitting or squatting position to an upright position, sudden stops after prolonged movement (e.g., after long-distance running), a crowded or stuffy environment, and emotional stress (e.g., nervousness caused by painful stimuli or a medical operation). Syncope may be more likely to occur under some special conditions such as vomiting, diarrhea, anemia, low iron stores, infection, menstruation, and the use of some drugs, such as diuretics, which can reduce blood volume or BP. When triggers cannot be completely avoided, more attention should be given to pediatric patients to prevent physical injury and psychological disorders associated with syncope [10] (I; C).

Identification of presyncope symptoms and physical counter-pressure maneuvers: when presyncope occurs, patients should adjust their position, such as changing to a sitting position or lying down, if possible. Most symptoms can be alleviated in a short time [128] (IIa; B). Physical counter-pressure maneuvers may avoid or delay the syncope by increasing peripheral venous return, such as slight bending of the knees, contracting abdominal muscles or limb muscles (hands clasped, elbow flexion, legs crossed, and toes dorsiflexion) after prolonged standing [10, 129–131] (I; C).

Maintaining psychological well-being: recurrent syncope may adversely affect the psychological well-being of patients, seriously affecting their quality of life, and even causing PPS [42] (IIa; B). Therefore, legal guardians/parents and healthcare staff should pay attention to the mental health of the patients. Patients should be informed that this type of syncope usually has a favorable prognosis and should be approached with a positive mindset. Patients are encouraged to communicate with others to relieve psychological stress. Legal guardians/parents should be suggested to comfort and support their children. If necessary, special psychological counseling or therapy should be recommended [132, 133] (IIa; B).

Appropriate physical exercise: appropriate exercise is beneficial in increasing pump function of limb muscle in patients with VVS, which is important for recovery. Regular physical exercise plans and exercise without obvious discomfort are recommended. Additionally, children with VVS are advised to do physical exercise under supervision [131].

Autonomic nervous function exercise

Upright training (tilt training) Patients are encouraged to stand upright against the wall with their feet approximately 15 cm away from the wall under supervision. The time for standing should be decided based on the tolerance and preference of the patient. Generally, the children may start from 5 minutes per session, twice daily, gradually increasing to 30 minutes per session [9] (I; C). Some biomarkers may help get a better effect of intervention from this measure [134–138] (IIa; B) (Table 4).

Dry towel wiping The forearms and both legs of the patient are recommended to be repeatedly wiped with a soft and dry towel. Five minutes is recommended for each part, twice a day [139] (I; C).

Increase the intake of water and salt

Adequate daily water intake up to 30–50 mL/kg/day (no more than 1500–1700 mL) is recommended to achieve a clear urine color. Salt intake can be increased through additional salt intake in daily meals or regular drinking of oral rehydration salts (ORS) for at least two months, after which re-evaluation should be conducted for the

Table 4 Biomarkers for predicting therapeutic outcomes in children and adolescents with vasovagal syncope

Biomarkers and cutoff values	Clinical significance
ECG acceleration index < 26.77 [134]	Upright training (tilt training) may be recommended
Night-time DBP standard deviation < 5.75 mmHg [137]	Upright training (tilt training) may be recommended
Night-time DBP variation coefficient < 13.2% [137]	Upright training (tilt training) may be recommended
24-h urine adrenaline < 5.53 μg [138]	Upright training (tilt training) may be recommended
Body mass index < 18.9 kg/m^2[144]	Oral rehydration salts may berecommended
24-h urine sodium < 83 mmoL [145]	Oral rehydration salts may berecommended
Flow-mediated vasodilation > 8.85% [150]	Midodrine hydrochloride may be recommended
Plasma CGRP level > 62.56 pg/mL [151]	Midodrine hydrochloride may be recommended
Serum uric acid < 299 μmol/L [152]	Midodrine hydrochloride may be recommended
HR increases before positive response in HUTT compared to the supine HR > 30 bpm [115]	Metoprolol may be recommended
24-h urinary norepinephrine > 34.84 μg [155]	Metoprolol may be recommended
Baroreflex sensitivity > 10 ms/mmHg [157]	Metoprolol may be recommended
LVEF > 70.5% [159]	Metoprolol may be recommended
LVFS > 38.5% [159]	Metoprolol may be recommended
Poincaré plot longitudinal/transverse axis ratio > 2.7 [160]	Metoprolol may be recommended

ECG electrocardiogram, *DBP* diastolic blood pressure, *CGRP* calcitonin gene-related peptide, *HR* heart rate, *HUTT* head-up tilt test, *LVEF* left ventricular ejection fraction, *LVFS* left ventricular fractional shortening

patients [140–142] (IIa; B). In hot weather seasons, excessive sweating or fluid loss may occur and further increase of water and salt intake is needed. The combination of hemoglobin and BMI values can provide a reference for the selection of ORS [143] (IIa; B). Certain biomarkers can predict that ORS has a better effect on VVS [142, 144–146] (IIa; B) (Table 4). Additionally, ORS is especially suitable for children with VVS-VI [147] (IIa; B), but is not recommended for patients with hypertension, kidney disease, or heart failure [1] (I; C).

Pharmacological intervention

Indications Children with recurrent syncope (more than twice every 6 months or more than three times per year), with risk of injury, and poor response to non-pharmacological therapy may be considered for pharmacological therapy [10, 148] (I; C).

Midodrine hydrochloride The initial dose ranges from 1.25 to 2.5 mg/time, once or twice daily. After 2–4 weeks, it can be increased to 2.5 mg/time, three times daily. During medication, the supine BP should be monitored; the dose should be reduced or discontinued when the supine BP increases significantly (above the 95th percentile of BP) [149] (IIa; B). Some biomarkers can predict that midodrine hydrochloride may lead to better outcomes of VVS cases [150–152] (IIa; B) (Table 4). Children with a baseline BP above the 95th percentile of the same age and sex and children who are allergic to this medicine should not use midodrine hydrochloride as treatment.

Metoprolol The initial dose is 0.5 mg/kg/day orally, twice daily, and can be gradually increased to a tolerable dose (no more than 2 mg/kg per day or the maximum adult daily dosage) [153] (IIa; A). Patients with significant sinus bradycardia, atrioventricular block (II or III degree), bronchial asthma, and allergy to drugs should be contraindicated to this therapy. Some biomarkers can predict the efficacy of metoprolol in such cases [115, 154–160] (IIa; B) (Table 4).

Other drugs Fludrocortisone may reduce the probability of VVS syncope events in children and adolescents [161] (IIa; B). There is limited experience regarding the application of sertraline in children and adolescents with VVS [162] (IIa; B), and it can be considered when other drugs are ineffective; however, side effects must be carefully monitored.

Pacemaker therapy and others

Most children with VVS have a good prognosis [31] (I; C). For patients with recurrent syncope accompanied by prolonged cardiac arrest (> 4 seconds) and those surviving cardiopulmonary resuscitation [10, 163, 164], pacemaker implantation can be considered under the recommendation of pediatric cardiovascular specialists [11], as it may reduce the incidence of syncope events [165]. Left atrial ganglion

catheter ablation can improve the symptoms of adults with VVS [166], and long-term follow-up of malignant VVS in children has achieved good results [167].

Postural orthostatic tachycardia syndrome

The complicated pathophysiology and heterogeneous clinical manifestations of POTS pose a challenge to the treatment [168–172] (IIa; B) and require a comprehensive treatment plan [28]. The management of POTS in children and adolescents involves health education, pharmacological therapy, and other strategies [173–178]. Biomarker-oriented individualized therapy is an important strategy for the treatment of POTS [4, 124, 125, 179, 180] (IIa; B). However, it is also essential to focus on the management of the comorbidities [181] (IIa; B).

Health education

Avoidance of triggers Patients should avoid prolonged standing, rapid changes in position from the supine or sitting or squatting to upright, taking drugs that aggravate symptoms, such as norepinephrine reuptake inhibitors, and being infected or fatigued [182] (IIa; B). Wearing compression garments can increase peripheral blood return and reduce orthostatic tachycardia caused by insufficient peripheral blood return [9] (I; C). At least 8 hours of sleep per day is also recommended [48, 173] (IIa; A). Patients with a salivary cortisol concentration > 4.1 ng/mL upon waking up in the morning had better sleep-stimulating treatment effects [183] (IIa; B).

Appropriate physical exercise It is recommended to establish regular physical exercise plans for children and adolescents [184] (IIa; B) and ensure aerobic exercise for 1–2 hours/day for at least 5 days a week under parental supervision. Exercise can increase the blood volume of children, increase the left ventricular end-diastolic volume and stroke output, and enhance muscle pump function, thus improving the tolerance of children to upright positions. Some children with POTS have obvious exercise intolerance, and their exercise prescription should be gradual. Children who cannot tolerate long-term orthostatic exercise (such as long-distance running and ball sports) should start with non-orthostatic exercise. After 1–2 months of tolerating non-orthostatic exercise, they can gradually transition to orthostatic exercise and slowly prolong the time for exercise. A physical exercise plan should last for at least 3 months to form a lifestyle of exercise. However, other treatments should be considered for children with contraindications to sports [48] (IIa; A).

Autonomic nervous function exercise

The protocols of autonomic nervous function exercise are the same as the corresponding part of the treatment of VVS. Children and adolescents suffering from POTS with QTd > 43 ms are recommended to receive the autonomic nervous function exercise [185] (IIa; B).

Increase salt and water intake

For managing POTS in children and adolescents, salt and water intake should be increased [186] (IIa; B). Some biomarkers can predict the fact that salt and water intake have better effects on POTS [187–190] (IIa; B) (Table 5). For children and adolescents with severe symptoms, intravenous saline infusion may relieve symptoms [9] (I; C).

Pharmacological intervention

Pharmacological intervention should be considered for children and adolescents with severe symptoms that significantly affect the quality of life.

Midodrine hydrochloride The initial dose ranges from 1.25 to 2.5 mg/time orally, once or twice per day, and can be switched to 2.5 mg/time, three times per day after 2–4 weeks if the effect is not observed. Also, special attention should be paid to BP monitoring [191–197] (IIa; B). Some biomarkers can predict the effects of midodrine hydrochloride prior to treating POTS [191–200] (IIa; B) (Table 5). Generally, midodrine hydrochloride may be more effective than metoprolol or ORS in the treatment of children and adolescents with POTS [201] (IIa; B). The best curative effect can be achieved after 3 months of treatment, while extending the treatment course to 6 months does not significantly improve the therapeutic effect [202] (IIa; B). The contraindications are mentioned above (see section "Pharmacological intervention" of "Vasovagal syncope").

Metoprolol The initial dose is 0.5 mg/kg/day orally, twice per day. This dosage can be gradually increased to a tolerable dose after 2–4 weeks but should be no more than 2mg/kg per day or the maximum adult daily dosage [1]. Some biomarkers can predict the effects of metoprolol [203–212] (IIa; B) (Table 5). A model with corrected maximum P-wave duration (ms), corrected minimum QT interval (ms), and Tped (ms) in ECG can predict the efficacy of metoprolol for children with POTS [209] (IIa; B). Metoprolol can reduce clinical symptom scores [201] (IIa; B). The contraindications are mentioned above (see section "Pharmacological intervention" of "Vasovagal syncope").

Table 5 Biomarkers for predicting therapeutic outcomes in children and adolescents with postural orthostatic tachycardia syndrome

Biomarkers and cutoff values	Clinical significance
MCHC > 347.5 g/L [179]	Increased intake of water and salt or oral rehydration salts may be recommended
24-h urinary sodium < 124 mmol [187]	Increased intake of water and salt or oral rehydration salts may be recommended
Body mass index < 18.02 kg/m^2 [188]	Increased intake of water and salt or oral rehydration salts may be recommended
Increase in HR (from the supine position to standing) > 41 bpm [189]	Increased intake of water and salt or oral rehydration salts may be recommended
The maximum HR during active standing test > 123 bpm [189]	Increased intake of water and salt or oral rehydration salts may be recommended
Baroreflex sensitivity > 17.01 ms/mmHg [190]	Increased intake of water and salt or oral rehydration salts may be recommended
Plasma copeptin level > 10.5 pmol/L [192]	Midodrine hydrochloride may be recommended
Increase in SBP (from the supine position to upright) ≤ 0 mmHg [193]	Midodrine hydrochloride may be recommended
Increase in DBP (from the supine position to upright) ≤ 6.5 mmHg [193]	Midodrine hydrochloride may be recommended
Flow-mediated vasodilation > 9.85% [196]	Midodrine hydrochloride may be recommended
Erythrocyte hydrogen sulfide production > 27.1 nmol/min/10^8 RBC [197]	Midodrine hydrochloride may be recommended
Plasma MR-proADM level > 61.5 pg/mL [199]	Midodrine hydrochloride may be recommended
Poincaré plot longitudinal axis < 573.9 ms and transverse/longitudinal axis ratio > 2.9 [200]	Midodrine hydrochloride may be recommended
Plasma copeptin level < 10.2 pmol/L [203]	Metoprolol may be recommended
Plasma C-type natriuretic peptide > 32.55 pg/mL [204]	Metoprolol may be recommended
Orthostatic plasma norepinephrine level > 3.59 pg/mL [205]	Metoprolol may be recommended
Baroreflex sensitivity > 8.045 ms/mmHg [206]	Metoprolol may be recommended
HR variability TR ≤ 33.7 and SDNN index ≤ 79.0 ms [207]	Metoprolol may be recommended
Baseline QT interval dispersion > 37 ms [208]	Metoprolol may be recommended
Corrected QT interval dispersion > 47.9 ms [208]	Metoprolol may be recommended
Corrected maximum P-wave duration > 109 ms, corrected minimum QT interval > 382.5 ms, and T-wave apex to T-wave end interval dispersion > 45.6 ms [209]	Metoprolol may be recommended
5-min HR at HUTT > 110 bpm [210]	Metoprolol may be recommended
10-min HR at HUTT> 112 bpm [210]	Metoprolol may be recommended
5-min HR difference from baseline HR at HUTT > 34 bpm [210]	Metoprolol may be recommended
10-min HR difference from baseline HR at HUTT > 37 bpm [210]	Metoprolol may be recommended
The product of HR and BP at 5-min during HUTT > 11,548.5 bpm × mmHg [211]	Metoprolol may be recommended
The product of HR and BP at 10-min during HUTT > 10,988.0 bpm × mmHg [211]	Metoprolol may be recommended

MCHC mean erythrocyte hemoglobin concentration, *HR* heart rate, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *RBC* red blood cell, *MR-proADM* mid-regional fragment of pro-adrenomedullin, *TR* triangulation index, *SDNN* standard deviation of all NN intervals, *HUTT* head-up tilt test

Management of comorbidities

Correcting iron and vitamin deficiencies may be beneficial in improving the symptoms of patients with POTS [213–215] (IIa; B). The evaluation and management of POTS comorbidities are also receiving increasing attention [182, 216]. Other common comorbidities of POTS include allergic diseases, migraines, mental disorders, sleeping disorders, hyperventilation syndrome, chronic fatigue syndrome, joint hypermobility syndrome, and gastrointestinal disorders. The treatment of POTS in children requires a comprehensive assessment of the comorbidities [184] (IIa; B).

Orthostatic hypotension

OH can be managed firstly using non-pharmacological measures, such as avoiding triggers, increasing water and salt intake, taking physical counter-pressure maneuvers, and

wearing elastic socks [217–219] (IIa; B). If non-pharmacological treatments are not effective, midodrine hydrochloride or fludrocortisone can be considered [2] (I; C).

Orthostatic hypertension

Non-pharmacological therapy [220], including health education and autonomic function exercise, can be used. Health education includes knowledge on avoiding prolonged standing or sudden changes in position (from supine or sitting or squatting to an upright position) and providing psychological assistance. Currently, no medicines have been recommended for the treatment of OHT in children. However, special attention should be paid to the possibility of developing primary hypertension during late adolescence or adulthood in children with OHT.

Other types of neurally mediated syncope

Children and adolescents with SS usually experience recurrent syncope under specific circumstances [57, 58] (IIa; B). For example, the treatment of micturition syncope is health education. It is suggested that the patient should not stand up abruptly when getting up in the morning and avoid holding urine for a long period. It is recommended to micturate in a squatting position. If a syncopal attack occurs during micturition, the witness should assist the patient to lay down in a safe and well-ventilated environment and retain a unobstructed airway for the patient. For children with breath-holding spells, only health education and an explanation of the prognosis of the disease are needed, which means that the parents should understand that the attacks are generally not life-threatening. During a breath-holding spell, the parents need to ensure that their child lies on his or her side to prevent trauma and aspiration.

Follow-up

The prognosis of most children and adolescents with VVS or POTS is generally good, but regular follow-up is still needed to get better outcomes [221–223] (IIa; B). A follow-up at 1–3 months after the initial diagnosis and treatment is recommended, and the interval for follow-up thereafter should depend on the symptoms of the patients. Children and adolescents with more than four episodes of syncope have a reduced symptom-free rate [224] (IIa; B), while those with cardiac arrest or convulsive events during HUTT do not indicate a poor prognosis [81] (IIa; B).

In the follow-up of VVS, the frequency and manifestations of symptoms, treatment compliance, and drug tolerance should be recorded. The recurrent onset of symptoms is the main factor affecting the quality of life of children and adolescents [132] (IIa; B). Supine mean arterial pressure in HUTT, baseline urine specific gravity, the standard deviation of average RR intervals in milliseconds, mean corpuscular hemoglobin, and demographic factors are associated with the risk of syncope or presyncope recurrence [80, 225, 226] (IIa; B). The evaluation of therapeutic efficacy should mainly focus on symptom control [205] (IIa; B). A symptom score, which is based on the frequency of syncopal episodes, has been used to evaluate the efficacy [143] (IIa; B). A negative response to HUTT is not recommended as an effective indicator for treatment.

In the follow-up of children with POTS, the OI symptom score is recommended as an indicator to judge the therapeutic effect, and a score reduction of ≥ 2 points is considered effective [192] (IIa; B). If the treatment effect is not good, the condition of the patient should be re-evaluated to ensure that the diagnosis is correct and the treatment plan adjusted [227] (IIa; B). In addition, the influence of comorbidity should be considered. The duration of symptoms before treatment and the maximum upright HR in a standing position can be used as independent indicators to estimate the long-term prognosis, with patients receiving conventional intervention for POTS generally experiencing satisfactory long-term outcomes [228] (IIa; B). A baseline plasma mid-regional fragment of pro-adrenomedullin > 61.5 ng/L indicates that midodrine hydrochloride has a favorable long-term effect [229] (IIa; B). In a questionnaire survey, a total of 86% of children and adolescents with POTS showed symptomatic remission 5 years after their initial diagnosis [230] (IIa; B).

Conclusions

In summary, based on the latest global research reports, the guidelines were updated. In terms of the diagnosis of NMS as well as its related disorders in children, the concepts of STS and SHT were introduced; and the comorbidities of NMS were emphasized. Regarding the management, the detailed rules and recommendations for some non-pharmacological therapies were refined and the management of comorbidities was highlighted. Specially, the newly discovered biomarkers that can be used to guide individualized treatment in recent years were summarized and recommended. Furthermore, specific suggestions were put forward for the follow-up process and efficacy evaluation. The new guidelines will provide comprehensive guidance and reference for the diagnosis and treatment of NMS in children and adolescents. It is expected that the guidelines will be further improved and perfected in the future clinical practice and related studies.

Acknowledgements We acknowledged Chinese Pediatric Cardiology Society, Chinese Pediatric Society, Chinese Medical Association; Committee of Pediatric Syncope, College of Pediatricians, Chinese Medical Doctor Association; Pediatric Cardiology Society, Beijing Pediatric

Society, Beijing Medical Association; Committee of Pediatric Cardiology, College of Cardiovascular Physicians, Chinese Medical Doctor Association. The panelists: Jin-Dou An, Xin-Jiang An, Jie Chen, Li-Qing Chen, Ming-Wu Chen, Shu-Qin Chen, Qi Chen, Yong-Hong Chen, Sun Chen, Zhi Chen, Adolphus Kai-tung Chau, Mao-Ping Chu, Hui-Ying Cui, Xiang-Yu Dong, Jun-Bao Du, Shu-Xu Du, Zhong-Dong Du, Hong-Yu Duan, Jun-Kai Duan, Lin Feng, Li-Jun Fu, Fang Gao, Lu Gao, Wei Gao, Fang-Qi Gong, Li Gu, Hong Gu, Yong-Hao Gui, Zhen-Hui Han, Bo Han, Ling Han, Bing He, Xue-Hua He, Zhi-Xu He, Xiu-Fen Hu, Yao-Fei Hu, Yi-Min Hua, Guo-Ying Huang, Hui-Tao Huang, Min Huang, Ping Huang, Xing-Yuan Huang, Yu-Juan Huang, Shou-Yuan Jiang, Hong-Fang Jin, Mei Jin, Yan-Zhe Lei, Bo Li, Fen Li, Li Li, Tao Li, Xiao-Ming Li, Xiao-Hui Li, Yan Li, Yun Li, Zi-Pu Li, Yong-Mei Liang, Ying Liao, Fang Liu, Wei Liu, Xiao-Yan Liu, Ya-Li Liu, Hui-Ling Lu, Hai-Tao Lv, Tie-Wei Lv, Lu-Yi Ma, Bao-Quan Pan, Xiang-Bin Pan, Si-Lin Pan, Yu-Sheng Pang, Hua Peng, Jin-Hua Piao, Ming-Yang Qian, Wei Qian, Yu-Ming Qin, Jie Shen, Lin Shi, Guo-Dong Song, Jing-Hui Sun, Kun Sun, Li-An Sun, Ling Sun, Yan Sun, Hong Tian, Jie Tian, Cheng Wang, Cui-Ling Wang, Hong Wang, Lei Wang, Li-Hong Wang, Lin Wang, Qin Wang, Shu-Shui Wang, Wen-Di Wang, Xiao-Ning Wang, Yi-Biao Wang, Jian-Xin Wu, Rong-Zhou Wu, Yu-Rong Wu, Kun Xia, Ting-Ting Xiao, Yan-Yan Xiao, Li-Jian Xie, Yu-Mei Xie, Chun-Hong Xie, Yan-Lin Xing, Zhen-Yu Xiong, Bao-Yuan Xu, Yi Xu, Hui Yan, Jian-Ping Yang, Shi-Wei Yang, Qi-Jian Yi, Xia Yu, Xian-Yi Yu, Yue Yuan, Du-Fei Zhang, Hong-Yan Zhang, Hui-Li Zhang, Kun Zhang, Li Zhang, Ming-Ming Zhang, Qing-You Zhang, Xi Zhang, Yan-Min Zhang, Yong Zhang, Zhi-Wei Zhang, Cui-Fen Zhao, Bin Zhou, Kai-Yu Zhou, Hua Zhu, Sheng-Dong Zhu, Jian-Xin Zhuang.

Author contributions WC, LY and WS contributed equally to this work. WC drafted and revised the manuscript, and carried out the evidence-based methodology. LY carried out the evidence-based methodology and revised the final manuscript. WS drafted and revised the manuscript. TH, HM, DXY, SL, LYQ, and SJH revised and suggested changes to the manuscript. DJB and JHF designed the manuscript and revised the final manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding This manuscript was supported by the National High-Level Hospital Clinical Research Funding (Multi-center Clinical Research Project of Peking University First Hospital; 2022CR59).

Data availability The data are available from the corresponding author on reasonable request.

Declarations

Ethical approval Not required.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. Author Jun-Bao Du is a member of the Editorial Board for *World Journal of Pediatrics*. The paper was handled by the other editor and has undergone a rigorous peer review process. Author Jun-Bao Du was not involved in the journal's review or decisions related to this manuscript. The authors have no conflict of interest to declare.

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