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Article

# 2018 Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents

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ABSTRACT

Syncope belongs to the transient loss of consciousness (TLOC), characterized by a rapid onset, short duration, and spontaneous complete recovery. It is common in children and adolescents, accounting for 1% to 2% of emergency department visits.Recurrent syncope can seriously affect children's physical and mental health, learning ability and quality of life and sometimes cardiac syncope even poses a risk of sudden death. The present guideline for the diagnosis and treatment of syncope in children and adolescents was developed for guiding a better clinical management of pediatric syncope. Based on the globally recent development and the evidence-based data in China, 2018 Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents was jointly prepared by the Pediatric Cardiology Society, Chinese Pediatric Society, Chinese Medical Association (CMA)/Committee on Pediatric Syncope, Pediatricians Branch, Chinese Medical Doctor Association (CMDA)/Committee on Pediatric Cardiology, Chinese College of Cardiovascular Physicians, Chinese Medical Doctor Association (CMDA)/Pediatric Cardiology Society, Beijing Pediatric Society, Beijing Medical Association (BMA). The present guideline includes the underlying diseases of syncope in children and

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adolescents, the diagnostic procedures, methodology and clinical significance of standing test and head-up tilt test, the clinical diagnosis vasovagal syncope, postural orthostatic tachycardia syndrome, orthostatic hypotension and orthostatic hypertension, and the treatment of syncope as well as follow-up.


## 1. Introduction

Syncope is a transient loss of consciousness (TLOC) and inability to maintain the posture due to transient global cerebral hypoperfusion; it is characterized by a rapid onset, short duration, and spontaneous complete recovery [1,2]. In children and adolescents, syncope is a common emergency, accounting for 1% to 2% of emergency department visits [1], and the incidence is higher in girls than boys [3–5]. The pathogenesis, etiology, diagnosis and treatment of pediatric syncope differ from that in adults. Recurrent syncope can seriously affect children's physical and mental health, learning ability and quality of life [6] and sometimes cardiac syncope even poses a risk of sudden death. Hence, to better guide the clinical diagnosis and treatment of pediatric syncope, this guideline for the diagnosis and treatment of syncope in children and adolescents was jointly prepared by the Pediatric Cardiology Society, Chinese Pediatric Society, Chinese Medical Association (CMA)/Committee on Pediatric Syncope, Pediatricians Branch, Chinese Medical Doctor Association (CMDA)/Committee on Pediatric Cardiology, Chinese College of Cardiovascular Physicians, Chinese Medical Doctor Association (CMDA)/Pediatric Cardiology Society, Beijing Pediatric Society, Beijing Medical Association (BMA).

## 2. Classes of recommendations and levels of evidence for the management of pediatric syncope

The classes of recommendations and levels of evidence for the management of pediatric syncope were weighed and graded according to predefined scales (Tables 1, 2) [1,7].

## 3. The underlying diseases of syncope in children and adolescents

The pediatric syncope is mainly related to vasovagal syncope (VVS), postural tachycardia syndrome (POTS), orthostatic hypotension (OH), orthostatic hypertension (OHT), situational syncope (SS), carotid sinus syndrome (CSS) and cardiac syncope or even with an unknown etiology. VVS is the common cause of syncope in children and adolescents. Cardiac syncope accounts for only about 2% to 3% of cases, and unexplained syncope accounts for about 20% [6] (IIa; A). The classification of underlying diseases of syncope in children and adolescents is shown in Table 3, with the abbreviations used hereafter.

Stewart et al. [8] indicates that VVS and POTS are mainly caused by abnormal autonomic nervous reflex regulation or autonomic nerve dysfunction, and most VVS cases represent functional diseases. Breath-holding spells in infancy may be a special type of NMS.

Cardiac syncope is mainly caused by the abnormal structure or rhythm of the heart [9]. Although cardiac syncope is a rare cause of pediatric syncope, it is associated with a high risk of sudden death and needs to be diagnosed as early as possible.

Other causes of TLOC, including epilepsy, metabolic disorders (such as hypoglycemia, hypoxemia, hyperventilation syndrome [10]), poisoning, transient ischemic attack of the vertebral basilar artery system, "pseudo-syncope" caused by psychological factors [6,11] and TLOC from head trauma are easily misdiagnosed as syncope in the clinic. These diseases do not produce transient cerebral ischemia, so they should be strictly differentiated from syncope (IIa; A).

## 4. Diagnosis

### 4.1. Diagnostic procedures

In Fig. 1, the diagnostic precedures consist of 3 steps [12].

**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 |
|---|---|
| Neurally-mediated syncope (NMS) | Vasovagal syncope (VVS) (Vasoinhibitory type, VVS-VI; Cardioinhibitory type, VVS-CI; Mixed type, VVS-M) |
| | Postural tachycardia syndrome (POTS) |
| | Orthostatic hypotension (OH) |
| | Orthostatic hypertension (OHT) |
| | Situational syncope (SS) |
| | Carotid sinus syndrome (CSS) |
| Cardiac syncope | Arrhythmia |
| | Structural cardiac or cardiomyopathy |
| Unexplained syncope | |

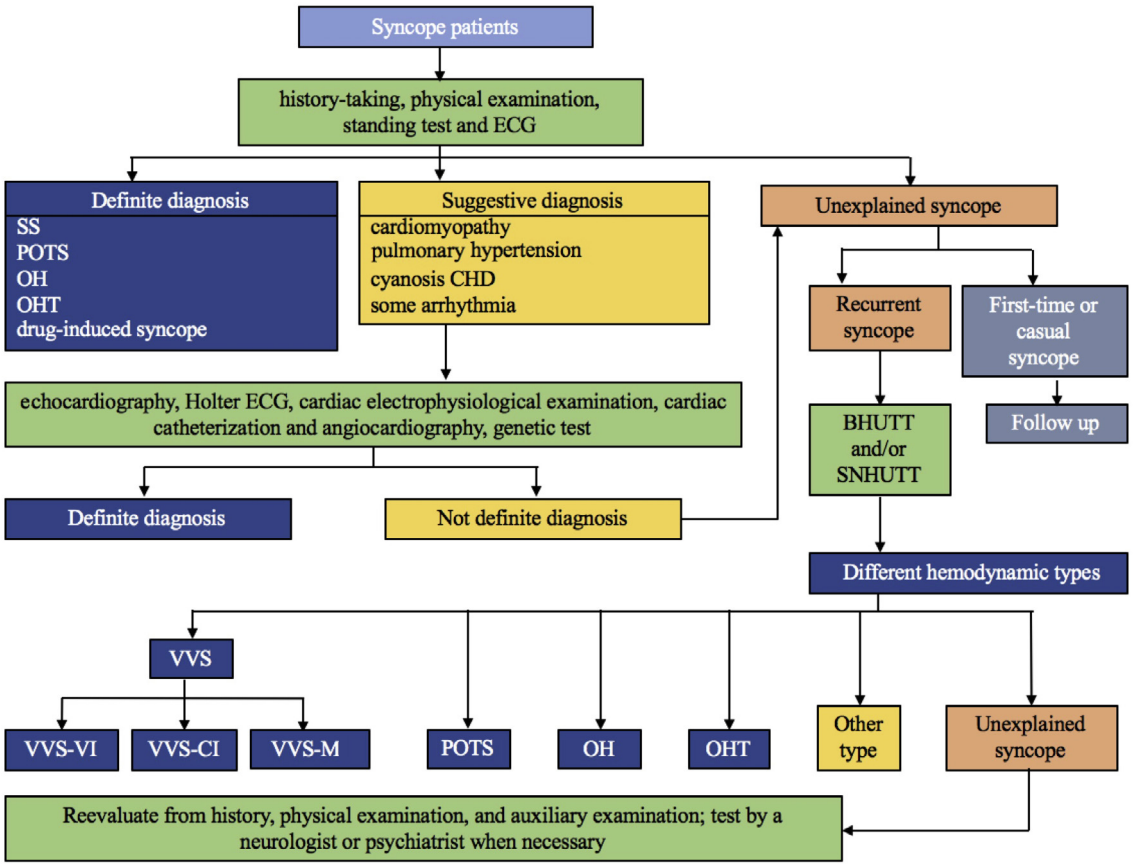


**Fig. 1.** (Color online) Diagnostic procedure for pediatric syncope. Echocardiography: For children with normal physical examination and normal routine electrocardiography (ECG) findings, echocardiography is generally not helpful to determine possible reasons. For children with possible structural heart disease after history-taking, physical examination and routine ECG, echocardiography is a screening tool to detect abnormal cardiac structures or functions. Holter ECG is a common test to determine the cause of syncope. However, because syncope is unpredictible, regular monitoring for 24 h only is difficult to confirm or thoroughly rule out the association between arrhythmia and syncope. Comprehensive judgment should be made together with the history-taking and other tests. Asymptomatic sinus bradycardia, atrioventricular block, and endless supraventricular or ventricular tachycardia may be possible reasons. For children with recurrent syncope, Holter ECG and loop event recorders have an important role in diagnosis and differential diagnosis. For children with syncope induced by sports and emotions, an exercise test should be performed to detect potential arrhythmias. For patients with suspected sick sinus syndrome, atrioventricular conduction abnormalities, and/or all ventricular and supraventricular arrhythmias, cardiac electrophysiological examination can be performed to ensure the diagnosis. For patients with suspected pulmonary hypertension or coronary heart disease (CHD), although echocardiography cannot clarify the diagnosis, cardiac catheterization and angiocardiography may be considered. For patients suspected of 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, genetic tests may help confirm the diagnosis. POTS: postural tachycardia syndrome; VVS: vasovagal syncope; OH: orthostatic hypotension; OHT: orthostatic hypertension; SS: situational syncope; BHUTT: basic head-up tilt test; SNHUTT: sublingual nitroglycerin head-up tilt test; M: mixed type; VI: vasoinhibitory type; CI: cardioinhibitory type.

In the first step [12], after the investigation of medical history, physical examination, supine and upright blood pressure (BP) as well as supine and upright ECG, the 3 diagnostic outcomes of patients can be obtained, definite diagnosis, suggestive diagnosis and unexplained syncope.

The patients with definite diagnosis after the first step sometimes include those with SS, POTS, OH, OHT and drug-induced syncope [12].

The patients with suggestive diagnosis after the first step as seen in Fig. 1 are in need of further laboratory investigations in step 2.

In the step 2 [12], cardiomyopathy, pulmonary hypertension, cyanotic congenital heart disease and some kinds of arrhythmias can be suspected by history-taking, physical examination and ECG findings. For example, infancy and early childhood onset, exercise-induced syncope, family history of structural heart disease or sudden death, and abnormal ECG findings can suggest cardiac syncope, with exercise-induced syncope and abnormal ECG findings giving the strongest clues [13–15]. For such patients, further examinations should be chosen to ensure the diagnosis, such as ECG, Holter ECG, loop event recorders, exercise test, echocardiography, intracardial electrophysiology, angiography, cardiovascular imaging and genetic tests, according to the specific situation [16] (IIa; A).

While, patients with unexplained syncope need head-up tilt test (HUTT) or follow-up [12–15]. The HUTT can help in the diagnosis of VVS and its hemodynamic types, vasoinhibitory type (VI), cardioinhibitory type (CI) and mixed type (M) [17,18], POTS [18–22], OH [21], or OHT [22] (IIa; A).

In step 3 [12], if, after the above steps are taken, a diagnosis is not possible, reevaluation is needed, including history-retaking, physical reexamination, and laboratory examinations. Also, assessment by a neurologists, endocrinologists or occasionally psychiatrists should be considered in step 3.

### 4.2. Methodology of standing test and HUTT

#### 4.2.1. Standing test

The standing test can be used for screening underlying causes of syncope or orthostatic intolerance (OI) in children. It has no specific contraindications.

*4.2.1.1. Standing test protocol.* In the standing test, first, the child lays supine for around 10–30 min for heart rate (HR), BP and ECG recordings. Then, the child is advised to stand for another 10 min, with simultaneous monitoring of HR, BP and ECG [20,22] (IIa; A).

*4.2.1.2. Clinical significance of standing test.* During the standing test, children should be closely observed to determine whether presyncope or syncope attacks and the test can help diagnose POTS [22], OH [23] or OHT [22,24]. Here, the presyncope consists of symptoms, including extreme light headedness, visual sensations, such as "tunnel vision" or "graying out" and variable degrees of altered consciousness without complete loss of consciousness. Patients with clinical manifestations of OI but a negative standing test result could perform the HUTT if they do not have contraindications (IIa; B).

*4.2.2. HUTT*

*4.2.2.1. Indications and contraindications for the HUTT.* Indications for the HUTT are [25] (1) clinically suspected VVS, POTS, OH or OHT, not confirmed by other tests; (2) a differential diagnosis with pseudo-syncope.

Contraindications for the HUTT are (1) syncope caused by aortic stenosis or left-ventricular outflow tract stenosis; (2) severe mitral stenosis with syncope; (3) syncope caused by pulmonary hypertension or right-ventricular outflow tract obstruction; (4) serious stenosis in the proximal coronary artery; (5) syncope caused by severe cerebrovascular diseases; and (6) syncope caused by definite arrhythmia.

*4.2.2.2. Preparation for the HUTT.* Test environment: quiet with dim light, comfortable room temperature, and no distractions.

Medicines and first aid equipment: nitroglycerin tablets for sublingual nitroglycerin provoked HUTT (SNHUTT), adrenaline, atropine, oxygen and defibrillator, etc.

Requirements for tilt bed: the bed should have supported foot pedals, fences on both sides, and fixed belts for chest and knee joints to avoid knee flexion and falling. The electric bed displacement should be smooth and rapid so that the bed can reach a 60° head-up tilt angle in 15 s [26] (IIa; B).

Operators: they should observe the details of the patient's performance during syncope or presyncope attacks and be familiar with the stopping rules and rescue program of the HUTT. The test must be stopped when children show a positive response (see Section 4.2.2.4) or have completed the whole 45-min process, or if the patient insists on stopping for any reason.

Detailed processes 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.

Informed consent: because the HUTT has a certain risk, such as fainting attack or severe hemodynamic or severe ECG abnormal findings, detailed instructions and risks should be described to children and their legal guardians/parents. Signed informed consent should be obtained before the test.

Preparation of children: any vasoactive drugs should be discontinued for at least five half-lives. Food (e.g., coffee) that might affect autonomic nervous system functions should be avoided. Children should fast for at least 4 h before the test. The test should be performed in the morning [27] without the presence of relatives [25] (Ia; C).

*4.2.2.3. Steps of the HUTT.* Basic HUTT (BHUTT) [18,26]: children should be on the tilt bed for around 10–30 min with the bands fixed to avoid buckling of ankle and knee joints. HR, BP and ECG recordings are taken during this period. Then, the bed is tilted upward at an angle of 60° with simultaneous monitoring of HR, BP and ECG. Finally, children should be placed in the supine position (from the upright position) at the termination of the test (see Section 4.2.2.4) (I; C).

SNHUTT: If syncope or pre-syncope does not develop with the BHUTT, children should undergo the SNHUTT, keeping the same position for a further 20 min after sublingual administration of nitroglycerin 4–6 μg/kg (maximum ≤300 μg). The endpoint of the test is a positive response or completion of the process. HR, BP, ECG and clinical performance should be recorded simultaneously after medicine administration [28] (IIa, A).

*4.2.2.4. Standards for a positive response.* VVS [15,28]: syncopal episodes or presyncopal signs (dizziness or vertigo, headache, chest tightness, palpitation, nausea, vomiting, paleness/pallor, sweating, blurred vision, hearing loss, or abdominal pain) 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 4–6 years old, <65 bpm for those 7–8 years old, and <60 bpm for those older than 8 years; (3) ECG showing sinus arrest, premature junctional contractions; and (4) atrioventricular block and cardiac arrest ≥3 s. The responses are classified as CI, VI, or M. VVS-VI is characterized by a significant decrease in BP without obvious HR reduction, VVS-CI by a marked HR decrease without marked BP decrease, and VVS-M by both a HR and BP decrease (IIa; A).

POTS [22,29]: supine HR is normal and during the initial 10 min of HUTT or the standing test, HR increases ≥40 bpm or is ≥130 bpm (in children 6–12 years old) or ≥125 bpm (in adolescents 13–18 years old), without orthostatic hypotension (BP decrease >20/10 mmHg) (IIa; A).

OH [23]: for classic OH, supine BP is normal and during the initial 3 min of HUTT or the standing test, SBP decreases at least 20 mmHg and/or DBP decreases at least 10 mmHg (IIa; C). While, the initial OH is defined with a transient BP decrease within 15 s after standing.

OHT [22]: supine BP is normal and during the initial 3 min of HUTT or the standing test, SBP increases ≥20 mmHg and/or DBP increases ≥25 mmHg (in children 6–12 years old) or ≥20 mmHg (in adolescents 13–18 years old) from supine to upright; or upright BP ≥130/90 mmHg (in children 6–12 years old) or ≥140/90 mmHg (in adolescents 13–18 years old) without an obvious change in HR (IIa; A). The above definition was first developed in children through a multi-center study in China [22].

*4.2.2.5. Characteristic HUTT results in children.* Children cooperate less during the test than do adults. Therefore, closely monitoring and trying to get the child's cooperation during HUTT is important. Arrhythmias, especially sinus bradycardia or junctional escape rhythm, are easily induced during the HUTT in children. ECG changes such as sinus arrhythmia and sinus bradycardia in HUTT can increase the probability of positive responses.

*4.2.2.6. Safety issue of HUTT.* HUTT should be performed according to the indications and operation steps to guarantee safety. HUTT may induce syncope, clinical symptoms can recur during the test, and the test can cause complications such as fear, transient aphasia [30], arrhythmias and convulsions. Despite a certain risk, in general, HUTT is safe when performed in accordance with the recommendations of the HUTT program and when syncope caused by organic heart diseases is excluded [25]. Long RR interval in ECG is common during the HUTT. Returning the patient quickly to the supine position can sometimes promote consciousness recovery. For children 6–18 years old, HUTT has high specificity, and no severe HUTT-related complications have been found [31] (IIa; B).

### 4.3. Clinical diagnosis

#### 4.3.1. VVS [15]

VVS (1) mainly occurs in older children; (2) is associated with predisposing factors in most patients, such as prolonged standing, emotional stress and crowded or stuffy environment; (3) is associated with a history of syncope; (4) features a positive hemodynamic response during HUTT (see Section 4.2.2.4); and (5) excludes other causes of syncope (IIa; A).

#### 4.3.2. POTS [20,22]

POTS (1) mainly occurs in older children; (2) is associated with the above predisposing factors in most patients; (3) is associated with OI symptoms, such as dizziness, headache, fatigue, blurred vision, chest tightness, palpitation, hand tremor, intolerance to movement and even syncope after an upright position; (4) is associated with a positive HUTT or standing test result (see Section 4.2.2.4); and (5) excludes other diseases that cause OI symptoms (IIa; B).

#### 4.3.3. OH [23]

OH (1) mainly occurs in older children; (2) is often associated with dizziness, vertigo, pallor, exercise intolerance, fatigue, blurred vision, chest tightness, palpitation, abdominal pain, nausea, vomiting, and even syncope after an upright position; (3) is associated with a positive HUTT or standing test result (see Section 4.2.2.4); and (4) excludes other diseases that cause OI symptoms (IIa; C).

#### 4.3.4. OHT [22]

OHT (1) mainly occurs in older children; (2) is associated with the above predisposing factors in most patients; (3) is often associated with dizziness, vertigo, pallor, exercise intolerance, fatigue, blurred vision, chest tightness, palpitation, abdominal pain, nausea, vomiting and even syncope after the upright position; (4) is associated with a positive HUTT or standing test result (see Section 4.2.2.4); and (5) excludes other diseases that cause OI symptoms (IIa; A).

## 5. Treatment

### 5.1. VVS

#### 5.1.1. Health education

After the diagnosis of VVS, education on syncope, including basic knowledge and skills in self-protection, is needed for patients and legal guardians/parents, which helps reduce syncope and the physical and psychological harm it causes. Education should include the following:

*5.1.1.1. Trigger avoidance.* VVS patients and their legal guardians/parents are advised to recognize the common triggers, such as prolonged standing, quick position change from a long lying or sitting position to an upright position, a crowded or stuffy environment, a sudden stop after long time moving (e.g., after a long run), and emotional stress (e.g., being nervous caused by pain stimuli or medical operations). In addition, syncope is prone to occur under some special conditions such as vomiting, diarrhea, anemia, low iron stores [32], infection, menstruation and the use of some drugs that could reduce blood volume or blood pressure (such as diuretics). Avoiding the common triggers can help reduce syncope; when factors cannot be completely avoided, we should pay more attention to patients to prevent accidental damage caused by syncope [33] (I; C).

*5.1.1.2. Identify presyncope symptoms and perform counter-pressure manoeuvres.* Presyncope symptoms are discomfort symptoms occurring in patients before syncope occurs, such as unexplained dizziness, chest tightness, palpitation, unclear vision, hearing loss, nausea, abdominal pain, vomiting, pallor and sweating. When presyncope occurs, patients should adjust their position, such as changing to a sitting position or lying down to rest if possible. Most symptoms can be relieved in a short time. In addition, counter-pressure manoeuvres may avoid or delay the syncope by increasing peripheral venous return, such as bending the knees slightly, contracting abdominal muscles or limb muscles (hands clasped, elbow flexion, legs crossed, and toes dorsiflexion) after prolonged standing [18,33] (I; C).

*5.1.1.3. Maintaining psychological well-being.* Recurrent syncope may adversely affect the psychological well-being of patients, which can seriously affect their quality of life and even cause pseudo-syncope. Therefore, legal guardians/parents and healthcare staff should pay attention to psychological health. Patients should be told that this kind of syncope usually has good prognosis, and it should be regarded with a healthy mentality. Patients are advised to communicate with others to relieve psychological stress. Legal guardians/parents should be told to comfort and encourage their children. Special psychological counseling or therapy should be performed if necessary [33,34] (I; C).

*5.1.1.4. Appropriate physical exercise.* There is no evidence that VVS patients need to avoid physical exercise. In contrast, appropriate exercise is beneficial to increase limb muscle pump function, which is important for recovery. Regular physical exercise plans are needed for these patients and to ensure daily aerobic exercise when monitoring patients [35] (IIa; C).

#### 5.1.2. Autonomic nervous function exercise

It has not been very clear whether tilt training is useful for VVS in children. Patients are encouraged to stand against the wall with feet left 15 cm from the wall under monitoring. Time for standing should be decided according to the tolerance and preference of the patient. Generally, the child may start from 5 min/time and twice a day, gradually increasing to 20 min/time [18] (I; C).

#### 5.1.3. Increase the intake of water and salt

Adequate water and appropriate salt intake is recommended or taking oral rehydration salts for 1 to 3 months but not in patients with hypertension, kidney diseases, or heart failure [36,37] (IIa; B).

#### 5.1.4. Pharmacological intervention

*5.1.4.1. Indications.* Indications include recurrent syncope (more than twice every 6 months or more than two or three times per year), presyncope with risk of injury and poor response to non-drug therapy [33] (I; C).

*5.1.4.2. Drug choice.* Zhang et al. first showed that midodrine hydrochloride was effective for treating pediatric VVS [38,39]. The initial recommended dose is 2.5 mg once or twice a day, increased to 2.5 mg three times a day, as necessary [38].

Metoprolol: for patients with HR increased by 30 times/min before a positive vasovagal response in HUTT (see in the Section 4.2.2.4), metoprolol is recommended [40], with the initial dose of 0.5 mg $kg^{-1}$ $d^{-1}$ in two divided doses gradually increased to a tolerance dose as necessary, which should not be >2 mg $kg^{-1}$ $d^{-1}$. Significant sinus bradycardia, atrioventricular block (≥2 degrees), bronchial asthma or drug allergy are the contraindications (IIa; B).

#### 5.1.5. Pacemaker therapy

Pacemaker therapy should be considered carefully. For recurrent syncope accompanied by a long cardiac arrest (>4 s), a

pacemaker should be considered under the advice of pediatric cardiovascular specialists [41,42] (IIa; C).

### 5.2. POTS

#### 5.2.1. Health education

*5.2.1.1. Avoidance of triggers.* Patients should avoid prolonged standing, fast position change from the supine or sitting upright, avoid taking the drugs that aggravate symptoms (such as norepinephrine reuptake inhibitors), and avoid being infected or fatigue. Wearing compression garments can increase peripheral blood return and reduce orthostatic tachycardia caused by insufficient peripheral blood return [18] (I; C). Counter-pressure manoeuvres such as leg crossing and squatting should be encouraged in children with warning symptoms.

*5.2.1.2. Appropriate physical exercise.* Patients should have regular physical exercise, choose proper exercise, and ensure daily aerobic exercise under monitoring but should avoid exercise with prolonged standing [18] (I; C).

#### 5.2.2. Autonomic nervous function exercise

This is recommended for children with POTS; especially those with corrected QT interval dispersion (QTcd) >43 ms should perform an autonomic nervous function exercise [43]. For methods, see the VVS part (IIa; B).

#### 5.2.3. Increase the salt and water intake

Children with POTS should increase the intake of salt and water, especially those with 24-h urinary sodium <124 mmol/L [44] or body mass index <18 kg/m$^2$ [45]. The recommended use of oral rehydration salts is the same as for VVS. Intravenous saline can alleviate symptoms in children [18] (IIa; B).

#### 5.2.4. Pharmacological intervention

For children with severe symptoms that affect the quality of life, poor non-drug therapy response, and risk of injury for unobvious presyncope, pharmacological intervention should be considered.

*5.2.4.1. Midodrine hydrochloride.* Midodrine hydrochloride is effective for some forms of pediatric POTS [46–51]. The initial dose usually is 2.5 mg once or twice a day, with an increase to 2.5 mg three times a day, as necessary [46–51]. BP should be monitored during the treatment. Hemodynamic indexes and biomarkers are useful for drug selection. Midodrine hydrochloride is indicated with flow-mediated dilation >9.85% [49], hydrogen sulfide production from erythrocytes >27.1 nmol/min [50], plasma midregional pro-adrenomedullin level >61.5 pg/mL [51], plasma copeptin level >10.5 pmol/L [46], pre-treatment increase of SBP $\leq$0 mmHg, or pre-treatment increase of DBP $\leq$6.5 mmHg (from the supine position to standing) [47] but with BP greater than the 95th percentile BP value by age and sex or with drug allergy (IIa; B).

*5.2.4.2. Metoprolol.* Metoprolol is effective for pediatric POTS [48], with the initial dose of 0.5 mg kg$^{-1}$ d$^{-1}$ divided into two administrations. The total dose of the drug should not be >2 mg kg$^{-1}$ d$^{-1}$. Metoprolol is indicated with plasma copeptin level <10.2 pmol/L [52], plasma c-type natriuretic peptide level >32.55 pg/mL [53], or orthostatic plasma norepinephrine level >3.59 pg/mL [54]. Severe sinus bradycardia, atrioventricular block, bronchial asthma and drug allergy are the contraindications (IIa; B).

## 6. Follow-up

The prognosis of most children and adolescents with VVS or POTS is good, but regular follow-up is needed. Effective medical disease-related information given to patients and their legal guardians/parents can reduce the onset of symptoms. A follow-up of 1–3 months after the initial diagnosis and treatment is indicated, and then the follow-up should depend on the onset of symptoms.

Follow-up of VVS should monitor the frequency and degree of symptoms, treatment compliance and drug tolerance. Recurrent onset of symptoms is the main factor affecting the quality of life of children and adolescents [34].

For POTS, Jin et al. first put forward a symptom score system (a modified Calgary score) to evaluate the outcome of POTS children [55]. The score system is recommended as an index for treatment efficacy and a score reduction of $\geq$2 points is considered effective [51]. The standing test is also used as an auxiliary index for evaluating treatment efficacy [56]. With poor therapeutic effectiveness, reevaluation is recommended for a correct diagnosis, timely adjustment of treatment (IIa; C) and to detect any psychological factors affecting the situation.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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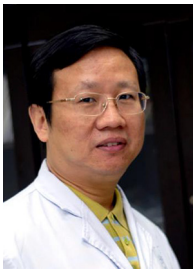

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