Evaluation, Diagnosis, and Treatment of Sydenham Chorea: Consensus Guidelines

Terrence Thomas, MD,[1] Michael Eyre, MD, PhD,[2,3] Emanuela Ferrarin, MSc,[4] Tamsin Newlove-Delgado, MD, PhD,[5] Adrian Sie, MD,[6,7] Thais Armangue, MD, PhD,[8] Hilla Ben-Pazi, MD,[9] Hanene Benrhouma, MD,[10] Antonio Clavenna, MD, PhD,[11] Francisco Cardoso, MD, PhD,[12] Leon S. Dure, MD,[13] Hannah F. Jones, MD, PhD,[14] Donald L. Gilbert, MD, MS,[15] Sheffali Gulati, MD,[16] Yuwu Jiang, MD, PhD,[17] Natalija Krajnc, MD, PhD,[18] Shekeeb S. Mohammad, MD, PhD,[19,20] Alessandro Orsini, MD, PhD,[21] Suvasini Sharma, MD,[22,23] Susan E. Swedo, MD,[24] Rachel Webb, MD, PhD,[25,26,27] Jo M. Wilmshurst, MD,[28] Ahmet Yaramis, MD,[29] Sanem Yilmaz, MD,[30] Sameer Zuberi, MD, PhD,[6,31] Michael Morton, MD, MPhil,[6] Russell C. Dale, MD, PhD,[19,20] Margherita Nosadini, MD, PhD,[32,33] Ming Lim, MD, PhD[3,34]

An international panel of 27 experts (pediatric and movement disorder neurologists, psychiatrists, and parent representatives) from all continents participated in a Delphi process to establish international consensus guidelines for the evaluation, diagnosis, and management of children with Sydenham chorea (SC) based on best evidence and expert opinion. In total, 88 recommendations reached consensus. Practitioners should identify key signs of SC (chorea and hypotonia), screen for behavioral, mobility, swallowing, speech, and cognitive impairments, and acute rheumatic fever (ARF) features including carditis. Etiological evaluation will differ according to population ARF risk. At all times, patients, families, and educators should receive support, information, and guidance to minimize the impact of SC on academic and social functioning. Antibiotic treatment is recommended at first presentation. Long-term secondary antibiotic prophylaxis should follow international or local guidelines, and measures to reduce pain and distress associated with intramuscular antibiotics will aid in adherence. Immunotherapy (corticosteroids) is recommended in moderate to severe SC. In those with inadequate recovery, intravenous immunoglobulin or plasma exchange should be given. In SC relapse, repeat clinical assessments, etiological investigation, and antibiotics plus corticosteroid therapy should be considered. This consensus guideline will standardize the evaluation and management of patients with SC and direct future research to improve the lived experience and outcomes of patients and families.

INTRODUCTION

Sydenham chorea (SC) is a major manifestation of acute rheumatic fever (ARF) characterized by a choreiform movement disorder, motor abnormalities, and neurobehavioral symptoms, occurring as a result of a dysregulated immune response to superficial Group A β-hemolytic streptococcal (GAS) infections.[1–3] SC primarily affects children living in low-resource regions and in indigenous populations[1–3] but still occurs in high-income nations, usually in underserved population groups.[3,4] The prevalence of rheumatic heart disease, the main sequela of ARF, has increased 1.5-fold since the 1990s and remains a health priority in specific populations around the world.[5–7]

abstract

[1]Department of Paediatrics, Neurology Service, KK Women's and Children's Hospital, Singapore; [2]School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom; [3]Children's Neurosciences, Evelina London Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [4]Centro di Riferimento Oncologico di Aviano IRCCS, Aviano, Italy; [5]Children and Young People's Mental Health (ChYMe) Research Collaboration, University of Exeter Medical School, Exeter, United Kingdom; [6]Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom; [7]NHS Lanarkshire, Bothwell, United Kingdom; [8]Neuroimmunology Unit, Sant Joan de Déu Children's Hospital, Esplugues de Llobregat, Barcelona, Spain; [9]Assuta Ashdod Hospital, Ashdod and Avertto Medical Ltd, Aderet, Israel; [10]Department of Child and Adolescent Neurology, Faculty of Medicine of Tunis, National Institute Mongi Ben Hamida of Neurology, University of Tunis El Manar, Tunis, Tunisia; [11]Laboratory of Child Health and Development Epidemiology, Department of Medical Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy; [12]Movement Disorders Unit Hospital das Clínicas, Federal University of Minas Gerais, Belo Horizonte, Brazil; [13]Departments of Pediatrics and Neurology, University of Alabama at Birmingham, Alabama; [14]Department of Neuro-services, Starship Children's Hospital, Auckland, New Zealand; [15]Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [16]Centre of Excellence & Advanced Research for Childhood Neurodevelopmental Disorders, Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; [17]Department of Pediatrics, Peking University First Hospital, Beijing, China; [18]Department of Pediatrics, General Hospital Slovenj Gradec, Slovenj Gradec, Slovenia; [19]The Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia;

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Expert consensus guidelines and various national guidelines address the evaluation, diagnosis, and antimicrobial treatment of ARF,[8–10] but there is limited guidance specifically for SC. In this consensus document, supported by the Sydenham's Chorea Association (https://sydenhamschorea.com), we aim to bridge this gap and address the evaluation, diagnosis, and management of children with SC. This work is informed by a recent systematic review and meta-analysis of clinical features, investigations, treatment responses, and outcomes in children with SC,[3] supporting the need to develop this guidance by consensus in light of some key diagnostic and management questions lacking in high-quality evidence.

METHODS

This consensus document adheres to the ACCORD (ACcurate COnsensus Reporting Document) format (Supplemental Materials).[11] A Delphi method was chosen in accordance with best practices for consensus guideline development.[12] This method follows a structured process with equity in members' inputs, perspectives, and participation, as well as anonymity in voting.[11,12]

SC Steering Committee

A 10-member steering committee with SC expertise, comprising a core group with additional expertise in either the conduct of international consensus guideline development (M.E., M.L., M.N., R.C.D., S.Z. and T.T.) or managing complex neuropsychiatric conditions (M.M., T.N.D.) and parent representation of the Sydenham's Chorea Association (A.S., E.F.) convened on February 21, 2020, affirmed the rationale and need for this consensus development, developed the study process (systematic review/meta-analysis followed by Delphi), established criteria for expert panel recruitment, and set the project timeline.

Systematic Review and Development of Preliminary Consensus Statements

From January to December 2022, the steering committee undertook a systematic review and meta-analysis to address gaps in the current literature evidence, including the most critical and controversial issues, and to inform statement development for the Delphi consensus process. This review, now published, constituted evidence synthesis for drafting consensus statements, including individual patient data meta-analysis from 1479 patients in 307 articles extracted from PubMed, Embase, CINAHL, Cochrane Library, and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde) databases and registers of clinical trials (search terms: [Sydenham OR Sydenham's OR rheumatic OR minor] AND chorea), from inception to 2022 (1325 from modern era since 1945).[3] The consensus statements were derived from key issues in the evaluation, diagnosis, management, and treatments identified in SC systematic review and meta-analysis undertaken by the steering committee,[3] pragmatically selected based on the clinical experience of the group. Statements were then formulated by the core group and presented to the steering committee for feedback, discussion, modification, and, finally, ratification. Additional statements were solicited from steering committee members on themes based on respective expertise and experience. A final and approved list of statements was then prepared for voting for Delphi round 1 (R1).

Delphi Panel Recruitment

The Delphi panel comprising the steering committee and additional members selected based on (1) research experience as identified from publications, (2) clinical expertise with SC patients, and/or (3) identified by national organization as lead. To avoid other potential bias in the selection process, careful attention was given to ensure involvement from both low- and high-resourced nations and adequate representation from all continents. Two parent representatives (A.S., E.F.) were members of the Sydenham's Chorea Association and participated voluntarily as members of the steering committee. The aims of the study and requirements from them as parent representatives were established at the outset. Invitations were made in early 2022 by email.

Planned Delphi Process

The Delphi exercise constituted 2 rounds of questionnaires followed by a third and final round for discussion and ratification of consensus statements. The first 2 rounds used an online survey tool (SurveyMonkey.com), and the final round was a 2-hour video conference (Zoom). For R1, panelists received an accompanying introductory document with links to a curated list of published SC literature and a summary of the then unpublished SC meta-analysis data.

The R1 questionnaire included key statements on definitions, care team members, clinical assessment including assessment scales, investigations, treatments, and areas of need and future research. Panelists were asked to evaluate each statement using a 5-point Likert scale ("Strongly Agree," "Agree," "Neutral," "Disagree," and "Strongly Disagree"). Consensus was defined as a 75% agreement ("Strongly Agree" or "Agree" votes) among panelists. Free text comments could be appended to statements in a comment box. Patterns and themes identified in free text responses were used to improve statements where appropriate. Statements reaching consensus were retained. Round 2 (R2) aimed to improve precision of R1 statements and evaluate emerging or additional themes as proposed by the expert panel. Statements that were significantly modified were deemed new items and included in R2 along with new statements developed from additional themes identified.

In the final round, statements reaching consensus were presented for discussion and ratification. Although this was an online meeting with open discussion, anonymity was preserved in the voting process, which was conducted in real time on the Slido platform (Slido.com). Prior to the final round, the steering committee also consulted a pediatric infectious disease specialist (R.W.) with experience in ARF and SC for guidance on statements that informed antimicrobial prescribing practice, and a senior pharmacologist with special expertise in antimicrobials and psychotropic medications (A.C.) to review all recommendations that involved pharmacotherapy. After the final round, key recommendations in the guidelines were crystallized into an algorithm and flowchart by the core group and circulated by email to all panel members for comments and modification.

RESULTS

Delphi Panel Demographics

The final panel of 27 members from Africa (2 members), Asia (7), Europe (11), North America (3), Oceania (3), and South America (1) consisted of 21 pediatric neurologists, a pediatric psychiatrist, an academic psychiatrist, a movement disorder neurologist, a pediatrician, as well as a pediatrician and a research support pharmacist who were also parent representatives of patients with SC (Supplemental Table 1). Twenty-five (92.6%) and all 27 (100.0%) completed R1 and R2 in May and December 2023, respectively.

Twenty-three (85.2%) attended the final round on video conference in April 2024, and the 4 absentee panelists ratified statements via email.

Delphi Results

Delphi R1 contained 110 voting statements and 3 open-ended statements, with 76 (69.1%) statements achieving consensus. Twenty-four R1 statements (7 with consensus) were significantly modified and reformulated into 20 new statements in R2. With 2 additional statements developed from emerging themes, 22 statements were evaluated in R2. In the final round, a further 4 modified statements, 3 new statements were evaluated, and 2 statements were removed. The final guidelines contained 88 statements and 4 accompanying tables that reached consensus. Definitions of disease severity and key definitions are shown in Table 1. Table 2A-D present the 88 recommendations that reached consensus pertaining to evaluation, diagnosis, and management of SC in children, and areas of need. Table 3 lists important differential diagnosis of SC, and Table 4 contains guidance on pharmacotherapy. Supplemental Table 2 is an advisory on risk assessment for sudden death associated with intramuscular injections in patients with SC with associated heart disease. Figure 1 is an algorithm that summaries the key steps in the evaluation, diagnosis, and management of children with SC.

DISCUSSION

This consensus guideline for the evaluation and management of children with SC is a global initiative by an international panel of pediatric neurologists, movement disorder neurologists, pediatric psychiatrists, and parent representatives, with representation and voice from regions with high SC incidence and insight from parents with a lived experience of SC. This document will be applicable in different health care settings. We followed a structured approach beginning with evaluation and diagnosis of SC, followed by investigations and management strategies, and finally a list of areas of need that will require further work. We also address the importance of recognizing and managing neurobehavioral involvement in SC and the impact this has on children and families living with SC. Although we propose best practice recommendations in evaluation and management, we acknowledge that access to investigations (eg, neuroimaging), therapy (eg, intravenous immunoglobulin or plasma exchange), and multidisciplinary expertise (eg, cardiology consultation or allied health professionals) may not be universally available.

New-onset chorea in a previously healthy child is the hallmark of SC, but the likelihood of SC will differ according to regional ARF prevalence.[1] In most cases, a careful clinical evaluation will provide sufficient information toward an SC or an alternative diagnosis. The recommendations are calibrated to allow for different approaches and discretion in the need for etiological investigations based on risk of ARF. In regions with high ARF incidence, SC would be the most likely etiology of acute chorea unless proven otherwise,[7] but in low-incidence regions, the importance of considering and ruling out differential diagnoses is higher. In a typical clinical presentation of SC in a high-incidence ARF population or a person with demographic risk factors for ARF, extensive laboratory tests and neuroimaging will usually not be required, whereas a magnetic resonance imaging (MRI) brain scan with MR angiography for cerebrovascular pathology (such as moyamoya syndrome), autoimmune and metabolic studies, and genetic evaluation for monogenic disorders of dyskinesia may be warranted in low-risk regions (Table 2A, 1.8 and 1.9 and Table 3).

SC should be differentiated from other poststreptococcal or postinfectious neuropsychiatric manifestations. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, or the more recent formulation of pediatric acute-onset neuropsychiatric syndrome, is represented by tics and not by chorea. Additionally, patients with SC typically have hypotonia or low muscle tone, including a rare but severe paralytic form of hypotonia and chorea known as chorea paralytica (Table 2B, 3.1.4 and 3.1.5). Positive findings from screening

TABLE 1. Definitions Used in the Consensus Statements

A. Disease Severity	mRS
MILD DISEASE Motor with/without behavioral or psychiatric symptoms *without* impact to activities of daily living, school and family life.	0–1 [0 = Normal 1 = No significant disability despite having symptoms]
MODERATE DISEASE Motor with/without behavioral or psychiatric symptoms *with* impact to activities of daily living, school and family life but not fulfilling criteria as in Severe Disease below.	2–3 [2 = Mild disability, but able to perform function or activity without assistance 3 = Moderate disability, and requires assistance to perform function or activity]
SEVERE DISEASE Motor with/without behavioral or psychiatric symptoms. May be considered when ≥1 of the following features are present: • Unable to walk unassisted or a bedridden patient • Unable to use hands to self-care or self-feed • Incomprehensible speech or unable to speak • Requiring nasogastric or parenteral feeding • Severe psychiatric symptoms requiring constant care and attention for safety	4–5 [4 = Moderate disability, unable to perform function or activity without full assistance 5 = Severe disability, requiring constant care and attention]
Other Definitions Used in the Statements	
B. Timeline for a therapeutic effect	A lack of functional recovery (chorea or behavioral/psychiatric symptoms remain intrusive or disabling) following 2–4 weeks of treatment initiation. This period can be shorter for patients with severe SC.
C. Relapse of SC	Recurrence of chorea or neurological symptoms lasting for >1 week (or shorter if associated with functional decline), after a period of stability or improvement of at least 1 mo.
D. Persistent chorea	Persistence of chorea beyond 12 mos despite best treatment with symptomatic medication(s) or if chorea re-emerges immediately after treatment discontinuation. This reflects the presence of non-reversible, permanent or residual brain injury resulting in the symptom of persistent chorea.
E. Subclinical carditis	Patients with a normal chest examination or auscultatory findings with echocardiography or Doppler evidence of a mitral or aortic valvulitis, within 12 weeks of onset of SC.

Abbreviations: ARF, acute rheumatic fever; mRS, modified Rankin Score; SC, Sydenham chorea.

for behavioral symptoms should ideally be followed by evaluation by mental health professionals or practitioners with experience in mental health assessments (Table 2A, 2.3). Emotional lability, anxiety, irritability, hyperactivity, and inattention are the commonest behavioral manifestations in SC (Table 2B, 3.3),[3] but a wide range of neuropsychiatric conditions, including psychosis, may be present in SC.[13] However, care should be taken when assigning diagnostic labels, as symptoms will likely change or resolve over time or with definitive treatments (Table 2B, 4.5).[14] In some patients, neuropsychiatric and cognitive symptoms may persist after dyskinesia resolves.[13,15] The clinical assessment should include an assessment for other features of ARF, including carditis, which may be present in up to 81% of patients with SC (Table 2B, 4.7 and 4.8).[1,16,17]

Assessment scales that guide decision-making and treatment should provide objective characterization of symptoms, functional disability, activity impairments, and progress over time. We advocate the use of the modified Rankin Scale, a practical and internationally used scale for neurological disability,[18] and also recognize the role of the Universidade Federal de Minas Gerais Sydenham's Chorea Rating Scale and the Red X Clinical Rating Scale for Sydenham Chorea, which require special expertise and experience, as best suited for centers specializing in SC (Table 2B, 4.1–4.4).[19,20]

At diagnosis, patients and families or caregivers should be provided with support, information, and education, as well as guidance for schools and educational professionals on how to minimize the impact of SC on academic and social functioning (Table 2C, 6.2). Management and interventions in patients with SC target a complete and early resolution of motor, neuropsychiatric, and cognitive symptoms, but if this is not possible, strategies to optimize physical, educational, and social functioning should be prioritized in discussion with the patient and family (Table 2C, 6.1).[6,10] An important concept that was deliberated at length was that of a time limit in which a decision needs to be made for an escalation in therapeutic interventions. Similar to the approach in autoimmune encephalitis,[21] the panel agreed that a lack of a functional recovery (in which chorea or behavioral/psychiatric symptoms remain intrusive or

TABLE 2A. Consensus Statements on Definitions, General Statements, and Care Team Members in the Management of SC	
Statements	**% Agreement (No. of Voters)**
Definitions	
A1. Timeline for a therapeutic effect and for treatment escalation (failure to respond to treatment): A lack of functional recovery (chorea or behavioral/psychiatric symptoms remain intrusive or disabling) after 2–4 weeks of treatment initiation is appropriate for considering failure to respond to treatment, and for potential treatment escalation. This period can be shorter for patients with severe SC. (S: Conditional; L: 5)	100% (25)
A2. Relapse of SC: Recurrence of chorea or neurological symptoms lasting for >1 week (or shorter if associated with functional decline), after a period of stability or improvement of at least 1 mo. (S: Conditional; L: 5)	96% (25)
A3. Persistent chorea: Persistent chorea after 12 mos despite treatment with symptomatic medication(s). (S: Conditional; L: 5)	100% (24)
General Statements on SC and ARF	
1.1 SC is an acquired movement disorder characterized by chorea (brief, involuntary, random, and irregular movements of the limbs and face), usually with neuropsychiatric symptoms (most frequently emotional lability) and hypotonia. (S: Strong; L: 1–2)	100% (24)
1.2 SC is one of the major clinical manifestations of rheumatic fever (ARF), diagnosed by the revised 2015 Jones Criteria. (S: Strong; L: 1)	100% (24)
1.3 The chorea in SC is sustained throughout most waking hours and present for most days in a week. (S: Strong; L: 1–2)	100% (25)
1.4 The first episode of SC typically has an onset in childhood; a first episode of SC in adults is rare but possible. (S: Strong; L: 1–2)	100% (25)
1.5 A throat infection (usually a GAS pharyngitis) commonly precedes SC, but the absence of history of a clinical infection does not rule out SC. (S: Strong; L: 1–2)	100% (23)
1.6 An SC diagnosis can be made in a child with chorea even without evidence of a recent or concurrent GAS throat infection. (S: Conditional; L: 1–2)	100% (23)
1.7 In a child with unexplained new onset chorea and without evidence of a recent or concurrent GAS throat infection, the presence of carditis would strongly support a diagnosis of SC. (S: Strong; L: 1–2)	100% (23)
1.8 In populations at moderate to high-risk for ARF, SC is an important cause of new-onset chorea in a child (≤18 y). (S: Strong; L: 2)	100% (23)
1.9 In populations at low-risk for ARF, alternative causes of chorea must be strongly considered in a child with suspected SC, especially in patients with atypical features for SC or absence of evidence of a recent or concurrent GAS infection. (S: Strong; L: 2)	100% (23)
Care Team Members	
2.1 A child with suspected or confirmed SC should undergo assessment by a pediatrician with experience in SC, or a pediatric neurologist. (S: Conditional; L: 5)	95.8% (24)
2.2 A child with suspected or confirmed SC should undergo cardiac assessment by a pediatrician with experience in SC, or a pediatric cardiologist. (S: Conditional; L: 5)	95.8% (24)
2.3 A child with suspected or confirmed SC should be screened clinically for comorbid mental health (emotional or behavioral) difficulties. Positive findings should lead to a mental health assessment, ideally by a specialist mental health professional with experience in neurology, or a pediatric psychiatrist. (S: Conditional; L: 5)	95.8% (24)
2.4 A child with suspected or confirmed SC should be screened clinically for problems affecting learning. Positive findings should lead to a learning or educational assessment, ideally by a neuropsychologist or a professional with expertise in learning difficulties, where available. (S: Conditional; L: 5)	100% (24)
2.5 A child with suspected or confirmed SC should be screened clinically for problems affecting global motor function, hand function and mobility. Positive findings should lead to a motor function assessment, ideally by a physiotherapist, occupational therapist, or rehabilitation specialist, where available. (S: Conditional; L: 5)	100% (22)

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TABLE 2A. Consensus Statements on Definitions, General Statements, and Care Team Members in the Management of SC (Continued)	
Statements	**% Agreement (No. of Voters)**
2.6 A child with suspected or confirmed SC should be screened clinically for problems affecting feeding and swallowing. In case of positive findings, a feeding evaluation should be offered, ideally by a speech and language pathologist/therapist or rehabilitation specialist, where available. (S: Conditional; L: 5)	100% (22)
2.7 A child with suspected or confirmed SC should be screened clinically for problems affecting speech and language. In case of positive findings, speech pathology evaluation may be offered, ideally by a speech and language pathologist/therapist or rehabilitation specialist, where available. (S: Conditional; L: 5)	100% (22)

Abbreviations: ARF, acute rheumatic fever; GAS, Group A β-hemolytic streptococcus; L, level of evidence; S, strength of recommendation; SC, Sydenham chorea.
Strength of recommendation: "strong" or "conditional" as per World Health Organization guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease. Levels of Evidence 1–5 (Oxford Centre for Evidence Based Medicine Working Group 2011). Further details in Supplemental Tables 3–5.

TABLE 2B. Consensus Statements on Clinical Assessments and Etiological Investigations in SC	
Statements	**% Agreement (No. of voters)**
Clinical Assessment	
3.1 In a child with suspected SC, a complete neurological examination should be carried out, and the following potential signs/symptoms should be specifically assessed and noted:	
3.1.1 Chorea, which can present as unilateral (hemichorea) or bilateral involvement of the limbs, trunk, face or tongue (a "darting tongue").	100% (23)
3.1.2 Presence of other types of movement disorders (eg, tics).	100% (23)
3.1.3 Motor impersistence (this may manifest as the "milkmaid's grip" sign).	100% (23)
3.1.4 Low muscle tone (ie, hypotonia); rarely, this can manifest as severe hypotonia with an inability to sustain tone and movement (chorea paralytica or *chorea mollis).*	100% (23)
3.1.5 Mobility impairment, in particular, whether the motor symptoms (chorea or hypotonia) result in a difficulty maintaining a sitting or standing posture, or manifest a difficulty in walking, especially with risk of falling.	100% (23)
3.1.6 The presence of speech and language impairments, in particular, impaired fluency or articulation, or incomprehensible speech.	100% (23)
3.1.7 Difficulties with feeding and swallowing, in particular, dysphagia, the requirement for nasogastric feeding, gastrostomy or parenteral nutrition. (for all statements, S: Strong; L: 1–2)	100% (23)
3.2 Abnormal behavior or neuropsychiatric symptoms frequently precede or are associated with chorea in SC. (S: Strong; L: 2)	100% (24)
3.3 Emotional lability, anxiety, irritability and hyperactivity-inattention are the commonest behavioral manifestations of SC. (S: Strong; L: 1)	100% (24)
Clinical Assessment Scales, Tools, and Procedures	
4.1 A validated and standardized scale should be used for the assessment of SC severity and related behaviors at acute disease onset and at follow-up visits. (S: Conditional; L: 5)	100% (24)
4.2 The mRS has clinical utility in the assessment of SC, especially due to its ease of use and despite its lack of specificity for SC. (S: Conditional; L: 5)	100% (24)
4.3 Other more detailed and SC-specific scales, such as the UFMG Sydenham's Chorea Rating Scale and the Red X Clinical Rating Scale for Sydenham Chorea, may be useful, especially in centers specialized in SC. (S: Strong; L: 3)	100% (24)
4.4 Standardized psychiatric and/or behavioral assessment tools should be used whenever appropriate (eg, Strengths and Difficulties Questionnaire). (S: Conditional; L: 5)	100% (24)
4.5 Formal psychiatric diagnoses should be used whenever appropriate (eg, DSM-5/*ICD-10* disorders) but consideration should be given to the potential for symptoms to be modified in the course of an acute episode and with resolution in later reviews (i.e. the neurobehavioral symptoms may resolve over time). (S: Conditional; L: 4)	100% (25)

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TABLE 2B. Consensus Statements on Clinical Assessments and Etiological Investigations in SC (Continued)	
Statements	**% Agreement (No. of voters)**
4.6 With the parents' consent and the child's assent, family or home videos of dyskinesia and/or abnormal behavior, or video recordings of the neurological or neuropsychiatric examination, have utility as assessment tools at baseline and at follow-up visits. (S: Conditional; L: 5)	100% (25)
4.7 A thorough cardiac assessment should include an ECG and echocardiography with doppler studies, as cardiac involvement, including subclinical valvular disease, is common in children with SC. (S: Strong; L: 5)	100% (25)
4.8 A careful physical examination is required to evaluate for other RF features as per the revised 2015 Jones criteria, as well as for differential diagnosis of chorea. (S: Strong; L: 5)	100% (25)
Investigations	
5.1 In a child with suspected SC, the investigations carried out should mainly aim at demonstrating a preceding streptococcal infection, actively assessing for the presence of other manifestations of RF and ruling out differential diagnoses (as per regional prevalence of conditions: see Table 3 for a list of important differential diagnoses). (S: Strong; L: 1–2)	100% (20)
5.2 Neuroimaging should be considered in children with new-onset chorea, depending on the level of confidence of SC diagnosis (typical/atypical clinical picture, presence/absence of other major manifestations of RF, evidence of preceding streptococcal infection) and risk stratification (low/high risk) for RF in the population. (S: Strong; L: 1–2)	100% (22)
5.3 If neuroimaging is indicated, MRI is the modality of choice; brain CT may be considered in case of unavailability of brain MRI. (S: Strong; L: 5)	100% (22)
5.4 Although abnormalities may be demonstrable by SPECT or PET in children with SC (ie, hypermetabolism and/or hyperperfusion of the basal ganglia in the acute phase), these are not routinely recommended in all patients. (S: Conditional; L: 5)	100% (22)
5.5 At the first presentation of SC, the following investigations have a *low* utility in the evaluation of children with suspected SC, although in specific circumstances they may be useful for ruling out differential diagnoses, especially in case of features atypical for SC:	
5.5.1 Electroencephalography, unless seizures or encephalitis are suspected as a differential diagnosis.	100% (22)
5.5.2 Lumbar puncture and cerebrospinal fluid analysis, unless encephalitis is a primary concern (ie, NMDAR encephalitis).	100% (22)
5.5.3 Anti-basal ganglia antibodies. (S: Conditional; L: 5)	100% (22)

Abbreviations: ARF, acute rheumatic fever; ECG, electrocardiography; CT, computed tomography; L, level of evidence; MRI, magnetic resonance imaging; NMDAR, N-methyl D-aspartate receptor; PET, positron emission tomography; S, strength of recommendation; SC, Sydenham chorea; SPECT: single-photon emission computed tomography.
Strength of recommendation: "strong" or "conditional" as per WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease. Level of evidence 1–5 (Oxford Centre for Evidence Based Medicine Working Group 2011). Further details in Supplemental Tables 3–5.

TABLE 2C. Consensus Statements on Pharmacotherapy in SC	
Statements	**% Agreement (No. of voters)**
General Statements on Management Approach and Goals	
6.1 The main goal of management is resolution of SC symptoms and an early return to normal physical, educational, and social functioning, where possible. If this is not attainable, then the management team should focus on strategies to optimize quality of life with regards to physical, educational and social functioning. (S: Strong; L: 5)	100% (21)
6.2 In all stages of disease, support, counseling, education and provision of up-to-date information on the condition to the family/caregivers and/or the patient are important. Information should be made available to guide education professionals to minimize the impact of SC in the school setting. (S: Strong; L: 5)	100% (21)
6.3 Behavioral problems, psychiatric symptoms and difficulties affecting schooling are common in children with SC. Management should address these issues adequately. (S: Strong; L: 5)	100% (21)
6.4 A child with SC should be assessed and offered physical therapy, occupational therapy, speech and language pathology therapy, and/or rehabilitation therapy as required. (S: Strong; L: 5)	100% (21)

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TABLE 2C. Consensus Statements on Pharmacotherapy in SC (Continued)

Statements	% Agreement (No. of voters)
Treatment with Antibiotic Agents	
7.1 In all children with SC, regardless of the presence of cardiac disease, antibiotic therapy is required to prevent recurrence of ARF and development or progression of rheumatic heart disease, as per existing recommendations for rheumatic fever. (S: Strong; L: 1)	100% (25)
7.2 Antibiotic therapy is not expected to shorten the duration of chorea in the first presentation of SC. (S: Strong; L: 1)	100% (24)
7.3 At the time of SC diagnosis, if there is no penicillin allergy, either a single dose of intramuscular benzathine benzylpenicillin G, or a 10-d course of oral penicillin V or oral amoxicillin should be given, even in the absence of a positive throat culture or cardiac disease (Table 4). (S: Strong; L: 1)	100% (25)
7.4 Long-term antibiotic prophylaxis to prevent future streptococcal infections should be used in all children with SC, even in the absence of cardiac disease (Table 4). (S: Strong; L: 1)	100% (23)
7.5 Duration of antibiotic prophylaxis is dependent on the presence of residual heart damage (valvular disease) as defined by the echocardiographic screening criteria by the World Heart Foundation (2023).[a] The American Heart Association/American Academy of Pediatrics guideline (2009) recommends that patients with no carditis may stop prophylaxis after 5 y or age 21 (whichever is longer), those with carditis but no residual heart disease (no valvular disease) should continue for 10 y or age 21, and those with carditis and residual heart disease (persistent valvular disease) should continue for 10 y or until 40 y of age (whichever is longer), or may require lifelong prophylaxis. Alternatively, national guidelines may better address local specific expertise and treatment decisions. (S: Strong; L: 5)	100% (24)
7.6 The main aim of long-term antibiotic prophylaxis is the prevention of carditis or worsening of heart damage in patients with rheumatic heart disease. (S: Strong; L: 1)	100% (23)
7.7 Long-term antibiotic prophylaxis may have a role in prevention of SC relapse. (S: Strong; L: 1)	100% (23)
7.8 For patients with non-immediate allergy to penicillin, a 10-d course of oral cephalexin (or other 1st generation cephalosporin) should be used at the time of diagnosis. For patients with immediate allergy to penicillin, an oral macrolide is recommended at the time of diagnosis. For secondary prophylaxis, a macrolide is recommended in case of penicillin allergy; oral sulfonamides may be considered if macrolides cannot be used. (S: Strong; L: 5)	100% (25)
7.9 Efficacy, accessibility, acceptance and adherence are key considerations when selecting the agent and mode of administration of long-term antibiotics as secondary prophylaxis in children with SC. This includes a risk evaluation for the use of intramuscular benzathine benzylpenicillin G in patients with SC with rheumatic heart disease (Supplemental Table 2). (S: Strong; L: 5)	100% (23)
7.10 Health care practitioners administering intramuscular antibiotics should have knowledge of, and consistently apply, strategies and measures to reduce pain and distress associated with the treatments. (S: Strong; L: 5)	100% (23)
Treatment with Immunotherapy Agents	
8.1 Patients with mild SC may not require immunotherapy. (S: Strong; L: 5)	100% (23)
8.2 Patients with moderate and severe SC should be offered immunotherapy. (S: Strong; L: 5)	100% (23)
8.3 Immunotherapy will likely shorten the duration of chorea at the first episode of SC. (S: Strong; L: 2)	95.8% (24)
8.4 Based on observational evidence, corticosteroid therapy at the first episode of SC is associated with a reduced risk of a future relapse. (S: Strong; L: 2)	95.8% (24)
8.5 Corticosteroids should be the preferred first-line immunotherapy in patients with SC, in the absence of contraindications. (S: Strong; L: 2)	100% (23)
8.6 IV methylprednisolone, oral prednisone/prednisolone or oral/IV dexamethasone are corticosteroids commonly used in patients with SC (Table 4). (S: Strong; L: 3–4)	100% (23)
8.7 Depending on severity and treatment response, prolonged use of corticosteroids may be considered, such as monthly IV methylprednisolone for 1–3 mos or oral prednisone/prednisolone for 1–3 mos (Table 4). (S: Strong; L: 3–4)	100% (23)

(Continued on next page)

TABLE 2C. Consensus Statements on Pharmacotherapy in SC (Continued)	
Statements	**% Agreement (No. of voters)**
8.8 In moderate to severe SC and the presence of a contraindication to corticosteroid therapy (eg, tuberculosis or infection risk), IVIG should be considered. (S: Strong; L: 5)	100% (23)
8.9 In moderate to severe SC and a failure of response to first-line immunotherapy, then an additional immunotherapy agent may be considered. (S: Strong; L: 3–4)	100% (22)
8.10 In moderate to severe SC and a failure of response to corticosteroid therapy, IVIG or plasma exchange can be considered as additional immunotherapy. (S: Strong; L: 3–4)	100% (22)
8.11 Second-line immunotherapy treatments (eg, rituximab or cyclophosphamide) are generally not required in moderate to severe SC. (S: Strong; L: 5)	100% (22)
Symptomatic Pharmacotherapy for Movement Disorder	
9.1 Symptomatic pharmacotherapy for movement disorder may not be required in children with mild SC. (S: Strong; L: 5)	95.8% (23)
9.2 Symptomatic pharmacotherapy for movement disorder should be offered to all children with moderate to severe SC, in addition to antibiotics and immunotherapy. (S: Conditional; L: 5)	95.8% (23)
9.3 Sodium valproate is useful for the symptomatic treatment of movement disorder in SC. (S: Conditional; L: 3–4)	100% (24)
9.4 The use of older antipsychotics (eg, haloperidol or chlorpromazine) in SC may be associated with more side effects. (S: Strong; L: 3–4)	100% (24)
Management of psychiatric symptoms	
10.1 Many psychiatric disorders associated with SC may be appropriately treated with psychological interventions that take account of the underlying immune-mediated etiology. Mental health interventions should consider the monophasic nature of the condition in the decision-making process in relation to the role and duration of pharmacotherapy. (S: Strong; L: 5)	100% (24)
10.2 Pharmacotherapy, overseen by a psychiatrist where available, for psychiatric symptoms may be considered based on the clinical picture and severity of psychiatric disturbances, with the aim of symptomatic relief. (S: Strong; L: 5)	100% (24)

Abbreviations: ARF, acute rheumatic fever; IV, intravenous; IVIG, intravenous immunoglobulin; L, level of evidence; S, strength of recommendation; SC, Sydenham chorea.
[a] This statement has been updated after the Delphi consensus process in accordance with the echocardiographic screening criteria by the World Heart Foundation.[17]
Strength of recommendation: "strong" or "conditional" as per WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease. Level of evidence 1–5 (Oxford Centre for Evidence Based Medicine Working Group 2011). Further details in Supplemental Tables 3–5.

TABLE 2D. Consensus Statements on SC Relapse and Area of Need	
Statements	**% Agreement (No. of voters)**
SC Relapse and Persistent Chorea	
11.1 SC symptoms may be exacerbated by pregnancy (chorea gravidarum) or the use of estrogen or estroprogestinic therapies. (S: Strong; L: 1–2)	100 (24)
11.2 In a relapse of SC (of any severity) in the presence of a concurrent GAS throat infection or ARF, immunotherapy may be considered. (S: Conditional; L: 5)	100 (24)
11.3 Immunotherapy is generally not indicated in patients with persistent or chronic chorea (as defined in statement A3 above) without evidence of concurrent GAS or ARF. (S: Conditional; L: 5)	100 (24)
11.4 Maintenance immunotherapy treatments (eg, rituximab, azathioprine, or mycophenolate) are generally not required in SC with relapses, or in SC with persistent chorea. (S: Conditional; L: 5)	100 (24)

(Continued on next page)

TABLE 2D. Consensus Statements on SC Relapse and Area of Need (Continued)

Statements	% Agreement (No. of voters)
Areas of Need and Future Study	
12.1 Areas of need in Sydenham chorea include:	
12.1.1 A more in-depth understanding of SC epidemiology and pathophysiology.	100 (24)
12.1.2 Longitudinal studies to identify SC patients' and families' needs of support in the short and long term and how each health and social system could best address these.	100 (24)
12.1.3 Exploring a presumed genomic susceptibility to ARF and SC, although no clear genomic risk factors have yet been consistently defined.	100 (24)
12.1.4 Developing a standardized, specific and user-friendly assessment scale including motor function and psychiatric symptoms.	100 (24)
12.1.5 High-quality studies on the role of secondary prophylaxis with antibiotics in SC in the prevention of relapse.	100 (24)
12.1.6 High-quality studies on the role of symptomatic treatments and immunotherapy in shortening chorea duration and in the prevention of relapse.	100 (24)
12.1.7 Further exploration of the relation between neuropsychiatric symptoms in SC and the concept of PANS/PANDAS.	95.8 (24)
12.1.8 Strategies and measures to reduce pain and distress associated with long-term intramuscular antibiotic prophylaxis.	95.8 (24)
12.1.9 Strategies and measures to improve adherence with long-term intramuscular antibiotic prophylaxis.	100 (23)
12.1.10 Feasibility and efficacy of vaccine development for the prevention of group A β-hemolytic streptococcal infections. (For all statements, S: Conditional; L: 5)	100 (26)

Abbreviations: ARF, acute rheumatic fever; GAS, Group A β-hemolytic streptococcal; L, level of evidence; PANS, pediatric acute-onset neuropsychiatric syndrome; PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections; S, strength of recommendation; SC, Sydenham chorea.
Strength of recommendation: "strong" or "conditional" as per WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease. Level of evidence 1–5 (Oxford Centre for Evidence Based Medicine Working Group 2011). Further details in Supplemental Tables 3–5.

TABLE 3. Differential Diagnosis for SC

Differential Diagnosis in Children Presenting With New-Onset Chorea
• Movement disorders Tic disorder, or Tourette syndrome Post-infectious movement disorder Genetic or familial non-neurodegenerative chorea (eg, pathogenic variants in *ADCY5*, *ATP1A3*, *FOXG1*, *NKX2.1 TITF1*, *SLC2A1*, *GNAO1*, *PDE10A*)
• Autoimmune disorders Autoimmune encephalitis (in particular anti-NMDAR, anti-$GABA_AR$ and anti-D2R encephalitis) Other systemic autoimmune disorders (e.g. systemic lupus erythematosus, antiphospholipid syndrome, central nervous system vasculitis, neuro-Behçet)
• Central nervous system infections Encephalitis (mycoplasma, herpes simplex virus, varicella zoster virus, Japanese encephalitis virus) Lyme disease
• Cerebrovascular disorders Cerebral arteriovenous malformations Moyamoya syndrome
• Endocrine disorders or acute metabolic deficiency Hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, vitamin B12 deficiency, and chorea gravidarum
• Neurodegenerative disorders, or inborn errors of metabolism Wilson disease Lesch-Nyhan syndrome Ataxia-telangiectasia Glycine encephalopathy
• Dyskinetic-choreoathetoid cerebral palsy
• Functional neurological disorder
• Drug side effects or intoxication
• Intracranial space occupying lesions (eg, tumors, abscess)

Abbreviations: ARF, acute rheumatic fever; GAS, Group A β-hemolytic streptococcal.
This list should serve as a guide to investigations in a patient suspected to have SC. In a low-risk region for ARF and in a population not known to have vulnerability to ARF, a more thorough diagnostic evaluation may be required. However, in a moderate to high-risk ARF region or population with vulnerability to Sydenham Chorea (eg, Indigenous Australian or South Indian) and evidence of a recent GAS infection, investigations can be tailored to local prevalence of the above conditions.

TABLE 4. Antibiotic and Immunotherapy Therapeutic Agents and Doses

Antibiotic Therapy at First Presentation

Medication	Indication	Dose/Mode of Administration
Oral penicillin V (phenoxymethyl penicillin)	Primary treatment	Children ≤ 27 kg: 250 mg 2 to 3 times daily, 10 d Children > 27 kg and adults: 500 mg given 2 to 3 times daily, 10 d Note: Refer local guidelines, as doses may vary in your region.
Oral amoxicillin	Primary treatment	50 mg/kg once daily or in 2 divided doses (maximum 1g), for 10 d Note: Refer local guidelines, as doses may vary in your region.
IM benzathine benzylpenicillin G	Primary treatment	Children ≤ 30 kg: 600 000 U Single dose Children > 30 kg and adults: 1 200 000 U single dose Note: Refer local guidelines, as doses may vary in your region.
Oral cephalosporin (preferred 1st generation, eg, cephalexin)	Primary treatment as an alternative if non -immediate penicillin allergy[1]	Cephalexin: 40 mg/kg/day in 2 divided doses (max 500 mg/dose), 10 d Note: Refer local guidelines, as doses may vary in your region.
Oral macrolides	Primary treatment as an alternative if immediate penicillin allergy[1]	Azithromycin: 12 mg/kg once daily (max 500 mg), 5 d Erythromycin (ethylsuccinate): 40 mg/kg/day in 2–3 divided doses (max 1 g/day), 10 d Clarithromycin: 15 mg/kg/day in 2 divided doses (max 500 mg/day), 10 d Note: Refer local guidelines, as doses may vary in your region.
Oral clindamycin	Primary treatment as an alternative if penicillin, cephalosporins and macrolides cannot be used.	20 mg/kg/day in 3 divided doses (max 1.8 g/day), 10 d Note: Refer local guidelines, as doses may vary in your region.

Notes:
1. Penicillin allergy should be reviewed (ideally by an allergist) and tests performed to confirm it, where required.
2. Erythromycin may be considered but has higher risk of gastrointestinal side effects.
3. Not recommended: Levofloxacin and Moxifloxacin (unnecessarily broad spectrum), Tetracyclines (high prevalence of resistant strains), Sulfonamides and Trimethoprim-sulfamethoxazole (do not eradicate GAS in pharyngitis), and Ciprofloxacin (limited activity against GAS).

Long-Term Antibiotic Prophylaxis

Medication	Indication	Dose/Mode of Administration
IM benzathine benzylpenicillin G[1]	Antibiotic prophylaxis	Children ≤ 30 kg: 600 000 units every 4 weeks[2] Children > 30 kg, adults: 1 200 000 units every 4 weeks[2] Note: Refer local guidelines, as doses may vary in your region
Oral penicillin V	Antibiotic prophylaxis	Children and adults: 250 mg twice a day Note: Refer local guidelines, as doses may vary in your region
Oral macrolides	Antibiotic Prophylaxis, as an alternative if Penicillin allergy	Erythromycin (ethylsuccinate): 40 mg/kg/day in 2–3 divided doses (max 1 g/day) Azithromycin: 12mg/kg once a day (max 500mg) (off label use, optimal use not well defined). Note: Refer local guidelines, as doses may vary in your region
Oral sulfonamides	Antibiotic prophylaxis, as an alternative if penicillin and macrolides cannot be used.	Sulfadiazine: children ≤ 27 kg: 500 mg once daily children > 27 kg: adults: 1 g daily Note: Refer local guidelines, as doses may vary in your region

Notes:
1. If intramuscular preparations are chosen, the use of an adjunctive local anesthetic should be considered.
2. Every 3 weeks if the patient experiences GAS infection of RF relapses despite full adherence to a 4-week regimen, or worsening cardiac status risk.
3. For amoxicillin no published data available on the efficacy for secondary prophylaxis.
4. Patients with breakthrough GAS pharyngitis on penicillin should be treated with an alternative agent such as clindamycin for the acute episode and then restart penicillin prophylaxis (consider switching to a 3-weekly regimen as in Note 2 above).

(References: Guidelines (AHA Gerber 2009,[23] Australia 2020,[9] New Zealand 2014[10]), EBM and clinical query databases (UpToDate,[41] BMJ best Practice,[42] Clinical Key,[42] Dynamed,[43] Lexidrugs[44])

(Continued on next page)

TABLE 4. Antibiotic and Immunotherapy Therapeutic Agents and Doses (Continued)		
Immunotherapy		
Medication	**Indication**	**Dose/Mode of Administration**
IV methylprednisolone	First-line immunotherapy	20–30 mg/kg/day (max 1 g/day) for 3–5 d
Oral prednisolone (or prednisone)	First-line immunotherapy: • Initial therapy as an alternative to IV methylprednisolone • For prolonged therapy in moderate to severe disease • Taper after IV methylprednisolone	2 mg/kg/day (max 60 mg/day) for 1 week (or longer for prolonged therapy), then gradually tapered (total duration 1–3 mos)
Oral or IV dexamethasone	First-line immunotherapy: • Initial therapy as an alternative to IV methylprednisolone or oral prednisolone • For prolonged therapy in moderate to severe disease	20 mg/m^2 (body surface area) per day (divided into 2 or 3 doses, max 12 mg 3 times per day) for 3 d 20 mg/m^2/day (divided into 2 or 3 doses, max 12 mg 3 times a day) for 3 d, every 3–4 weeks (pulsed therapy); total duration 1–3 mos
Oral deflazacort	First-line immunotherapy: • Initial therapy as an alternative to IV methylprednisolone • For prolonged therapy in moderate to severe disease • Taper after IV methylprednisolone	0.9 mg/kg/day for 1 week (or longer for prolonged therapy), then gradually tapered (total duration 1–3 mos)
Therapeutic plasma exchange	First-line immunotherapy	One course is typically 5–7 single or double plasma volume exchanges over 7–10 d
IV immunoglobulin	First-line immunotherapy	2 g/kg over 2–5 d
Selected references: Paz JA, et al. *Pediatr Neurol.* 2006;34(4):264–9[26]; Walker K, et al. *J Child Neurol.* 2012;27(2):147–55[29]; Dean SL, Singer HS. *Tremor Other Hyperkinet Mov (N Y).* 2017;7:456[30]; Teixeira AL, et al. *Expert Rev Neurother.* 2021 Aug;21(8):913–922[2]		
Abbreviations: IV, intravenous; GAS, Group A β-hemolytic streptococcal; RF, rheumatic fever.		

disabling) following 2 to 4 weeks of treatment would be grounds to consider an escalation in immunotherapy interventions (Table 1). In severe SC, where there is loss of mobility, loss of upper limb function for self-care or feeding, loss of speech and communication or swallowing, or severe psychiatric symptoms with concerns for safety, this period of initial observation after a first immunotherapy treatment can be considerably shorter.

Antibiotic pharmacotherapy is recommended at diagnosis as a precautionary measure in all patients with SC, independently of microbiological confirmation of streptococcal throat infection (Table 2C, 7.1). In SC, the preceding GAS pharyngitis is usually a past and remote event, and evidence for a recent streptococcal infection is usually not available in the majority of patients (85% in total but mainly by serological testing; by positive throat culture for GAS in only 37%).[3] In the absence of penicillin allergy, a single dose of intramuscular benzathine benzylpenicillin G, or a 10-day course of oral penicillin V or amoxicillin remain treatments of choice. Oral cephalexin (or other first-generation cephalosporin) or a macrolide may be used in the presence of a nonimmediate or immediate allergy to penicillin, respectively (Table 2C, 7.8).[22]

Long-term secondary antibiotic prophylaxis (SAP) for secondary prevention of GAS infection is recommended in all children with SC even in isolated SC without ARF,[23] as there is a 72% decrease in the odds of SC relapse based on observational data,[3] in addition to prevention of rheumatic heart disease acquisition or progression.[1,6,8,17] Guidance for long-term SAP, which is predicated on the presence and severity of rheumatic heart disease, should follow established international guidelines, or local clinical practice guidelines where necessary. For example, in New Zealand, 10 years of SAP are recommended for ARF with mild or no carditis.[10] During the Delphi process, the expert panel referenced the SAP guidelines by the 2009 American Heart Association,[23] but there has been a recent update to the echocardiographic diagnosis of rheumatic heart disease by the World Heart Federation in 2023,[17] and thus statement 7.5 has been amended accordingly.

Adherence to long-term SAP is a key issue affecting its outcomes. Education of patients and families in this regard and measures to reduce pain if an injectable antibiotic is used may result in better adherence and are therefore recommended.[24,25] Addition of a local anesthetic (lidocaine, also known as lignocaine) to the injectable solution helps in reducing injection pain.[10,26] Other strategies to minimize pain and injection-related distress (eg, distraction techniques) may be considered in addition, but not in substitution, to lidocaine in the injectable solution.[24] Health care practitioners administering intramuscular antibiotics should have knowledge of, and consistently apply, strategies and measures to reduce pain and fear. Where major concern exists for injectable long-acting benzathine

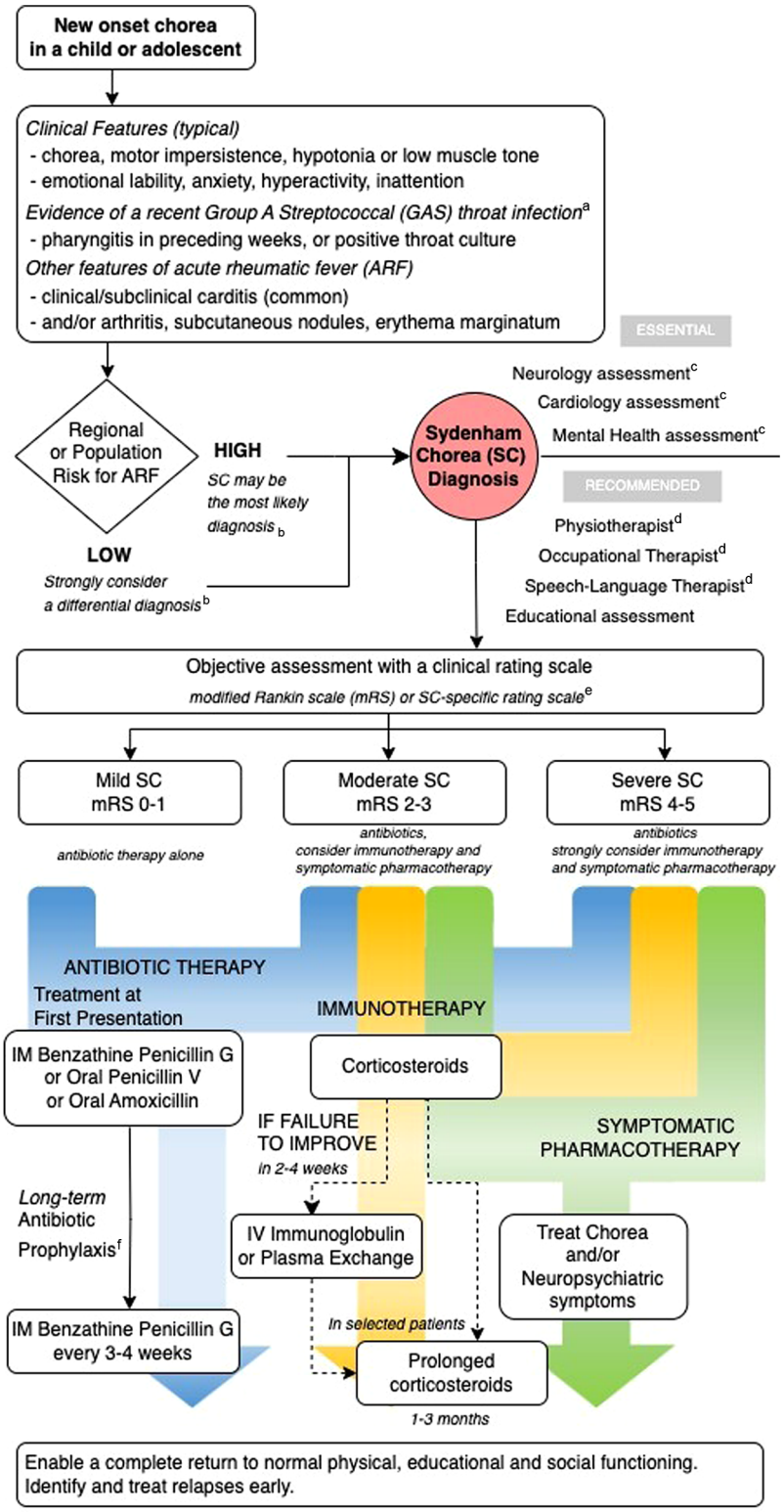

FIGURE 1.

Algorithm for the evaluation, diagnosis and management of patients with SC.

[a]Evidence of a recent GAS may not always be present. [b]See Table 3 for a list of differential diagnoses. [c]Or pediatrician or physician with experience in SC. [d]Or rehabilitation therapist, where available. [e]UFMG Sydenham's Chorea Rating Scale and the Red X Clinical Rating Scale for Sydenham Chorea. [f]See Table 2C, 7.5; for drug doses, see Table 4.

Abbreviations: ARF, acute rheumatic fever; GAS, Group A β-hemolytic streptococcus; IM, intramuscular; IV, intravenous; mRS, modified Rankin Score; SC, Sydenham chorea.

benzylpenicillin, oral antibiotic alternatives may be considered.[25] Recommendations for risk mitigation against sudden cardiac deaths with the use of intramuscular injections in patients with established rheumatic heart disease should be applied in accordance with available evidence.[27]

There was consensus that immunotherapy may not be required in mild SC, where symptoms are present without causing disability, but should be considered for patients with moderate disease and strongly considered for those with severe disease (Table 2C, 8.1 and 8.2 and Figure 1). Corticosteroids, administered as intravenous (IV) methylprednisolone, oral or IV dexamethasone, oral prednisolone/prednisone, or deflazacort (Table 3 for dose recommendations), are the preferred first-line immunotherapy agents with consensus that treatment for 1 to 3 months (depending on disease severity) would shorten the duration of chorea[3,28] and reduce the risk of relapse (Table 2C, 8.3–8.7).[3] It should be highlighted that these recommendations are based on 1 small randomized controlled trial,[28] observational data, and the meta-analysis as published,[3] and the quality of evidence is therefore not strong. Adequately powered randomized controlled trials, such as the planned TREAT-SC study (NCT06259006), are needed to clarify the need for immunotherapy in mild, moderate, or severe SC. If corticosteroids are contraindicated, then IV immunoglobulin should be used as an alternative first-line immunotherapy (Table 2C, 8.8).[29] There was also consensus for the use of additional immunotherapy with either IV immunoglobulin or plasma exchange when there is a lack of significant functional recovery within 2 to 4 weeks of corticosteroid therapy, as well as a consensus that second-line immunotherapy (eg, rituximab or cyclophosphamide) is generally not required in SC (Table 2C, 8.9–8.11).

Evidence for symptomatic pharmacotherapy for movement disorders in SC is largely based on observational data.[3] A wide range of therapeutic agents have been used over time, the choice of which appears to still be driven from the experience of the physician or of the care institutions, or from the availability of the therapeutic agent itself.[30] This may have been reflected in our consensus process, where a wide selection of therapeutic agents (sodium valproate, carbamazepine, levetiracetam, diazepam, clonazepam, phenobarbital, tetrabenazine, pimozide, haloperidol, chlorpromazine, fluphenazine, risperidone, diphenhydramine, hydroxyzine) were rated in the R1, with the question "which of the following agents would you consider for the symptomatic treatment of movement disorder in SC considering the benefit-side effect profile." Only sodium valproate reached consensus for this question as well as in the reformulated R2 statement (Table 2C, 9.3). However, the use of sodium valproate needs careful consideration, as has been done in epilepsy, in light of regulatory body warnings for teratogenicity risks to off-spring in both male and female patients.[31] These risks should be adequately and explicitly discussed with patients and their families. If valproate is prescribed, teratogenicity risk may be minimized with lower effective therapeutic doses ($\leq$600 mg/d)[32], short duration of use (typically $\leq$6 months of therapy in SC as opposed to prolonged therapy in epilepsy), education of adolescents regarding teratogenicity risks, and the use of pregnancy prevention measures in women of childbearing age.

Full consensus was also reached for the potentially increased risk of side effects with dopamine antagonists (eg, haloperidol or chlorpromazine) (Table 2C, 9.4), which is in keeping with a finding of increased risk of side effects such as dystonia and parkinsonism with neuroleptics in SC.[33] Our results are in line with recent reviews and expert opinions,[2,30,34–37] where antiseizure medications (valproate, carbamazepine, or levetiracetam) are preferred over dopamine antagonists and dopamine-depleting agents (eg, tetrabenazine), except where antiseizure medications have failed or are not available, or in more severe cases. Nevertheless, there is a pressing need to acquire more evidence to support this recommendation.[35–37] The use of symptomatic treatments alleviates the disability arising from the movement disorder, whereas immunotherapy acts to modify the underlying cause of disease progression and potentially limit the severity and duration of the illness. In patients with moderate to severe disease, the combination of both therapies is often necessary (Figure 1).

Pharmacotherapy for psychiatric symptoms may also be necessary in some patients and should be guided by a psychiatrist or mental health professional, taking into account the underlying disease (Table 2C, 10.1 and 10.2).

In the event of an SC relapse (Table 1), a repeat clinical assessment and severity scoring is warranted. An alternative etiology should be considered (eg, moyamoya syndrome, benign hereditary chorea, functional disorder), particularly if etiological investigations (Table 3) were incomplete at first diagnosis or in patients with an atypical clinical presentation. Antibiotic therapy plus first-line immunotherapy (prescribed in a similar way to the first episode) should be considered, but second-line or maintenance immunotherapy is not recommended (Table 2D, 11.2–11.4). Relapses will need to be differentiated from an exacerbation of symptoms associated with pregnancy or with estrogenic or estroprogestinic therapies (Table 2D, 11.1). When there is evidence of GAS reinfection associated with relapses, a shortening of the benzylpenicillin SAP interval should be considered (eg, moving from 4 weeks to 3 weeks) or a resumption of SAP, if this has been stopped.[6,9,17]

Persistent chorea, where dyskinesia persists as a long-term symptom in the absence of ongoing immune dysregulation, was defined in the literature as being a persistence of chorea for 24 months.[38] The expert panel voted on a shorter

time duration of 12 months (Table 2A, A3), which is consistent with a similar definition in the encephalitis literature.[21] As with relapse, a thorough re-evaluation for an alternative etiology should be considered in patients with persistent chorea (Table 3). Immunotherapy is not advised in patients with persistent chorea (Table 2D, 11.4).

The last group of statements addresses areas of need that will require future research. Among key statements, there was consensus for a deeper understanding of SC epidemiology and pathobiology (Table 2D, 12.1.1) and the needs of patients and families localized to their respective health and social systems (Table 2D, 12.1.1). Although no genomic basis has yet been defined, further research should be undertaken to unravel genomic (including epigenetic) risk predilection for ARF and SC (Table 2D, 12.1.3).[39,40] Standardized and specific rating scales for both motor and psychiatric symptoms of SC are required, with utility and applicability across well-resourced, resource-limited, and research settings (Table 2D, 12.1.4). High-quality studies are needed to better define the roles of immunotherapy, symptomatic pharmacotherapy, and secondary antibiotic prophylaxis in the prevention of relapse (Table 2D, 12.1.5 and 12.1.6). Finally, there is a pressing need for strategies and measures to improve adherence to long-term antibiotic prophylaxis, including the issue of pain and distress associated with intramuscular injections (Table 2D, 12.1.8 and 12.1.9).

This consensus guideline has several limitations. Mindful that there is a lack of high-quality data to guide recommendations, especially with regard to immunotherapy treatments and symptomatic treatment of motor and neuropsychiatric symptoms, the steering committee was careful to ensure that the statements remained anchored to insights from the meta-analysis and data synthesis[3] and prepare for randomized controlled trials, some of which are currently underway. The international panel of experts and parent representatives was heterogeneous in terms of health care setting and world regions but was able to achieve consensus that guides a consistent evaluation and treatment of patients with SC in high- and low-risk ARF regions. However, these recommendations are still vulnerable to bias and opinion based on experts' individual experience in treating complicated and atypical patients with SC. Although we endeavored to provide guidance for pharmacotherapy in Table 4, there will invariably be differences in local dosing recommendations and practice, and this should supersede the dose recommendations we have provided.

Despite these limitations, this consensus guideline will begin to standardize the evaluation, care, and management of patients with SC and provide the direction for future research and evidence to improve the lived experience and outcomes of patients with SC and their families.

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ABBREVIATIONS

ARF: acute rheumatic fever
GAS: Group A β-hemolytic streptococcal
IV: intravenous
MRI: magnetic resonance imaging
R1: round 1
R2: round 2
SAP: secondary antibiotic prophylaxis
SC: Sydenham chorea

[20]*Kids Neuroscience Centre, The Children's Hospital at Westmead, Faculty of Medicine and Health, University of Sydney, NSW, Australia;* [21]*Pediatric Neurology, Pediatric University Department, Azienda Ospedaliero Universitaria Pisana, University of Pisa, Pisa, Italy;* [22]*Neurology Division, Department of Paediatrics, Lady Hardinge Medical College & Associated Kalawati Saran Children's Hospital, New Delhi, India;* [23]*Division of Neurology, The Hospital for Sick Children, Toronto, Canada;* [24]*Department of Health and Human Services, Pediatrics and Developmental Neuropsychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland;* [25]*Department of Paediatric Infectious Diseases, Starship Children's Hospital, Te Whatu Ora-Health New Zealand, Auckland, New Zealand;* [26]*Department of Paediatrics, KidzFirst Children's Hospital, Te Whatu Ora-Health New Zealand, Auckland, New Zealand;* [27]*Paediatrics, Child and Youth Health, The University of Auckland, Auckland, New Zealand;* [28]*Department of Paediatric Neurology, Red Cross War Memorial Children's Hospital, Neuroscience Institute, University of Cape Town, Cape Town, South Africa;* [29]*Pediatric Neurology Clinic, Private Office, Diyarbakir, Turkey;* [30]*Department of Pediatrics, Division of Pediatric Neurology, Medical Faculty, Ege University, İzmir, Turkey;* [31]*Paediatric Neurosciences Research Group, Royal Hospital for Children, Glasgow, United Kingdom;* [32]*Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua, Padua, Italy;* [33]*Neuroimmunology Group, Paediatric Research Institute Città della Speranza, Padua, Italy; and; and* [34]*Department of Women & Children's Health, School of Life Course & Population Sciences, Faculty of Life Sciences and Medicine, King's College, London, United Kingdom*

Address correspondence to: Terrence Thomas, MD, Department of Paediatrics, Neurology Service, KK Women's and Children's Hospital, 100 Bukit Timah Rd, 229899 Singapore. Terrence.Thomas@singhealth.com.sg

Dr Thomas was a member of the steering committee and drafted the Delphi statements, manuscript, tables and figure. Dr Nosadini drafted the Delphi statements and contributed intellectual content to the manuscript, tables, and figure. Dr Lim led the steering committee and panel meetings and contributed intellectual content to the Delphi statements, manuscript, tables, and figure. Drs Eyre and Dale contributed intellectual content to the Delphi statements, manuscript, tables and figure. Ms Ferrarin and Drs Sie, Morton, Newlove-Delgado, and Zuberi were members of the steering committee and contributed intellectual content to the manuscript, tables, and figure. Drs Clavenna and Webb reviewed and finalized all pharmacological recommendations and drug doses presented in this document and contributed intellectual content to the final manuscript, tables, figure, and supplementary materials. All authors participated in virtual meetings, contributed intellectual content, and approved the final manuscript, tables, figure, and supplementary materials.

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