

Treatment of Sydenham's Chorea: A Review of the Current Evidence

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Abstract

Background: Sydenham's chorea (SC), the neurologic manifestation of rheumatic fever, remains the most prevalent form of chorea in children. Suggested treatments of chorea in SC include prophylactic penicillin, symptomatic (antipsychotic and anticonvulsant) medications, and immunomodulatory therapy (steroids, intravenous immunoglobulin (IVIG), and plasma exchange). In this manuscript, we undertook a systematic review of the published literature to examine the data supporting these therapeutic recommendations.

Methods: A search of PubMed, Embase, Psycinfo, and clinicaltrials.gov was conducted for publications pertaining to the treatment of SC/rheumatic chorea from 1956 to 2016.

Results: Penicillin prophylaxis appears to reduce the likelihood of further cardiac complications and the recurrence rate of chorea. Data on symptomatic therapy for chorea are limited to individual case reports or series and rare comparison studies. The efficacy of steroid use is supported by a single placebo-controlled study and several case series. Information on other immunomodulatory therapies such as IVIG and plasmapheresis are limited to a small number of reports and a single comparison study.

Discussion: Treatment decisions in SC are currently based on the treating physician's clinical experience, the desire to avoid side effects, and the existence of only limited scientific evidence. Based on a review of the available literature, chorea often improves with symptomatic therapy and immunotherapy tends to be reserved for those who fail to respond. Steroids are beneficial; however, data using IVIG and plasmapheresis are very limited. Larger, well-controlled studies, using standardized assessment scales, are required if therapeutic decisions for SC are to be based on meaningful information.

Keywords: Sydenham's chorea, rheumatic chorea, treatment, immunomodulatory, valproic acid, antipsychotic

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Introduction

***"The formulation of the problem is often more essential than its solution, which may be merely a matter of mathematical or experimental skill"* Albert Einstein**

Sydenham's chorea (SC), one of the major criteria for the diagnosis of rheumatic fever, is the most common form of autoimmune chorea. The typical age of onset of SC is 5–15 years and females are more affected than males. Chorea usually develops 4–8 weeks after a group A beta-hemolytic streptococcal (GABHS) pharyngitis; this is later than other manifestations of rheumatic fever, such as carditis or arthritis, which usually develop 2–3 weeks after infection. Classically, chorea in

SC is generalized; however, hemi-chorea occurs in about one-quarter of patients. Although symptoms can be mild, even in these instances difficulty with grooming, feeding, and handwriting can interfere with daily activities in school or work. Other neurologic symptoms in SC can include motor impersistence, hypometric saccades, reduced muscle tone, tics, clumsiness, dysarthria, and weakness. In rare instances the associated hypotonia can be so profound as to be completely disabling, a variant known as chorea paralytica or chorea mollis. Neuropsychiatric symptoms, including obsessive compulsive behaviors, personality changes, emotional lability, distractibility, irritability, anxiety, age-regressed behaviors, and anorexia, are common and frequently predate the appearance of chorea.¹ After improvement of their motor symptoms,

many patients with SC continue to have a high rate of anxiety and depression² as well as difficulty with cognitive tasks requiring attention and processing speed.³ Cardiac involvement, especially affecting the mitral valve, occurs in about two-thirds and arthritis in about one-third of SC patients. Patients initially presenting with only chorea but no other symptoms of rheumatic fever may develop cardiac involvement during a recurrence.⁴ Classically, SC is expected to resolve in 1–6 months. A retrospective study of 90 patients showed complete remission of motor symptoms in 85% by 6 months, and an additional 5% had complete remission by 1 year.⁵ In contrast, other groups have reported a greater persistence of motor symptoms in their populations. One prospective study of 32 patients with SC, followed for more than 2.5 years, found that symptoms persisted for 2 years or more in 50% of their cases.⁶ No predictive demographic features for a prolonged course were identified. Additionally, recurrences of chorea are not uncommon, occurring in 15–40% of patients.^{5,7} Identified triggers for relapses have included poor prophylactic penicillin adherence,⁵ the use of oral contraceptive agents, and pregnancy.⁸ Investigative laboratory studies assist in eliminating alternative causes of chorea, but do not confirm the diagnosis. Elevated antistreptococcal titers are present in about 15–30% and imaging is usually normal, except for possible acute phase enlargement of the basal ganglia and increased T2 intensity in rare cases.⁹ Persistent magnetic resonance imaging changes have been reported, particularly in patients with recurrent episodes of chorea.¹⁰

Pathophysiologically, acute SC is believed to be associated with antibodies against GABHS that cross-react, through the process of molecular mimicry, with either neuronal extracellular surface and/or intracellular (cytoplasmic or cytoskeletal) antigens. Initial evidence for an autoimmune disorder was based on the presence of immunoglobulin G reactivity to neuronal cytoplasm in human caudate and subthalamic nuclei that correlated with the severity and duration of symptoms.¹¹ Subsequent studies have shown that both acute sera and monoclonal (mAB 24.3.11) antibodies in SC patients activate Ca²⁺/calmodulin-dependent protein kinase (CaMKinase) II activity in a human neuronal cell line (SKNSH).^{12,13} This activation is believed to cause clinical symptoms by altering neuronal cell signal transduction, especially involving dopamine.¹⁴ Serum antibodies have also been identified in enzyme-linked immunosorbent assay titers against dopamine D1 and D2 receptors;^{15–17} attempts to confirm binding to D1 and D2 receptors in their conformational states in human cell lines have been mixed.^{16,18} These results provide theoretical support for trials of immunomodulatory therapies in SC.

Proposed treatments of chorea in SC currently include acute and prophylactic penicillin therapy, symptomatic medications, and possibly immunomodulatory therapy. The list of suggested symptomatic therapies is broad and contains the off-label use of anticonvulsants (valproate, carbamazepine) and neuroleptics (pimozide, haloperidol, risperidone, olanzapine). Once the patient becomes symptom free for at least 1 month, it is suggested that medications be gradually tapered. In the case of uncontrolled or persisting chorea, recognizing the proposed autoimmune etiology for SC, reports have recommended the use of steroids, intravenous immunoglobulin (IVIG) or plasma exchange. The

goal of this report was to systematically review the evidence for the use of antibiotics, symptomatic, and immunomodulatory therapy for the treatment of chorea in SC. Therapies for neuropsychiatric symptoms commonly seen in individuals with SC are not covered in this review.

Methods

“Science is a method to keep yourself from kidding yourself”

Edwin Land

Separate online searches were conducted using PubMed, Embase, Psychinfo, and clinicaltrials.gov in March 2017 for the years 1956 to 2016. The collection of references was restricted to human trials using the keywords “Sydenham’s” or “Sydenham” or “rheumatic chorea” and “treatment” or “antipsychotic”, “antipsychotics”, “antiepileptic”, “antiepileptics”, “immunosuppressive”, “AED” (antiepileptic medication), “AEDs”, “haloperidol”, “pimozide”, “risperidone”, “olanzapine”, “carbamazepine”, “valproic acid”, “valproate”, “steroid”, “steroids”, “methylprednisolone”, “prednisone”, “corticosteroid”, “corticosteroids”, “immunoglobulin”, “IVIG”, “plasmapheresis”, or “plex” but not “Huntington.” Manuscripts primarily focused on other diseases, without abstracts, or written in a language other than English were excluded. The same strategy was used for the collection of references from each database, i.e., PubMed (2,280); Embase (355), and Psychinfo (183). Clinicaltrials.gov was also searched, but no additional studies of interest were identified. From a total of 2,780 identified references (including duplicates), 71 articles were selected for further review, 44 being directly related to treatment.

Results

“Not everything that can be counted counts, and not everything that counts can be counted” Albert Einstein

Quality of assessments and use of rating scales. The methodologies used to assess clinical symptoms and outcomes in the reviewed references varied widely. In 30 studies, the authors merely reported qualitative improvement,^{10,19–46} and only one included an unbiased observer.²³ One report used the Modified Abnormal Involuntary Movement Scale, which is intended for tardive dyskinesia.⁴⁷ Five reports used unverified scales that were designed based on prior literature;^{48–52} and only four used the Universidade Federal de Minas Gerais Sydenham’s Chorea Rating Scale (USCRS).^{53–56} The USCRS was published in 2005 and subsequently recommended as the optimal scale for the assessment of clinical symptoms in SC.⁵⁷

Another significant deficit in multiple reports is the failure to provide sufficient information on the time course of improvement. For example, reports varied on whether they provided the time to improvement of symptoms (10 out of 44),^{19,25,27,30,35–38,42,55} the time to full remission of symptoms (two out of 44),^{21,28} or both (13 out of 44).^{20,22–24,26,32,33,35,41,44–46,52,53} Nine out of 38 studies reviewed improvement in a chorea score at fixed weekly, monthly, or yearly intervals, rather than reporting the time to an observed improvement or recovery.^{29,40,47–51,54,56} Twenty-eight out of 44 reported the total length of time treatment was provided.^{20,22–30,32–36,38,44–46,48–56}

Antibiotic treatment and prophylaxis. Despite the fact that patients commonly do not have an active infection at the time of the appearance of chorea, most published treatment recommendations include a 10-day course of oral penicillin or a single intramuscular (IM) dose of penicillin at the time of SC diagnosis.⁵⁰ Sulfa drugs are commonly used for those individuals with a penicillin allergy. In the reviewed literature, only four papers (11 patients) reported throat culture results at the time of diagnosis (five positive, six negative).^{28,32,34,45,52}

Secondary prophylaxis to prevent future streptococcal infections is advocated. More specifically, the World Health Organization recommends 1.2 million units of penicillin G administered IM every 21 days. The duration of treatment is dependent on the severity of cardiac involvement. Patients with no carditis may stop prophylaxis after 5 years or age 18 (whichever is longer), those with mild carditis should continue for 10 years or age 21, and those with moderate to severe carditis should receive lifelong prophylaxis.⁵⁸ However, this literature review identified significant diversity of antibiotic treatment and/or reporting. Twenty-one studies failed to comment on whether primary or secondary penicillin treatment was utilized^{19–21,23,25,26,29,31,33–36,39,45,46,48,51,54–56} and 10 reports did not comment on the length of treatment or method of delivery.^{22,24,28,35,40,42–44,51,53} One study reported primary but not secondary penicillin treatment.⁴⁷ Studies that reported penicillin use varied in terms of its method of administration; either oral or IM primary penicillin therapy preceding IM prophylaxis,^{10,32,37,49,50} or in the substitution of amoxicillin followed by prophylaxis with feneticillin. One report specifically noted that although secondary prophylaxis with penicillin was recommended to all patients, it was not received in most.³⁰ One patient reportedly received no antibiotics, although this was not intentional.²⁷ One patient underwent tonsillectomy for repeated infections, but the use of antibiotic treatment was not described.⁴¹

Secondary antibiotic prophylaxis has been shown to reduce the risk of new cardiac lesions associated with recurrent rheumatic fever. The effect of prophylaxis on the recurrence of chorea, however, is less clear. In a prospective study of 31 SC patients in Chile, all undergoing monthly prophylaxis with benzathine penicillin G, 17 separate recurrences of “pure” chorea were detected in 10 individuals (six girls), with data collection being adequate in 16 out of 17 occurrences.⁵⁹ In four out of 16, the recurrence was associated with either high stationary antistreptococcal antibody levels or a sudden rise in levels followed by a decline prior to the exacerbation. In eight out of 16 recurrences, there were modest elevations in levels (antistreptolysin O (ASO) 50–133 Todd units, median 100; antiDNaseB 170–680, median 170). In four out of 16 there was no evidence of a recent streptococcal infection or elevated titers. In a similar study performed in Jerusalem, 10 out of 19 SC patients (seven females) developed a total of 11 recurrences of chorea.⁷ Only six out of 11 recurrences were associated with either poor penicillin adherence or an increase in ASO titers. These reappearances of chorea were not predictable by either prior rheumatic fever activity or cardiac findings. In contrast, a retrospective study of 90 SC patients in Turkey showed that those adherent to their

secondary prophylaxis regimen had a significantly lower recurrence rate (nine out of 82 patients) than those who had only irregular prophylaxis (five out of eight patients).⁵ In another study, penicillin adherence rates in all patients with SC were 71% (61 out of 85) and 53% (nine out of 17) in patients with recurrent chorea and adequate follow up information.⁶⁰ Hence, available data suggest that prophylaxis likely reduces the rate of recurrence, but it does not completely prevent it.

Symptomatic treatment

Dopamine antagonists. Several dopamine antagonists have been utilized in worldwide studies to treat chorea, the most common being the neuroleptics haloperidol and pimozide (Table 1). In 1972 haloperidol (4–5 mg daily, divided twice a day or three times a day) was successfully used in two patients that had previously failed phenothiazine, diazepam, sedation, and/or amantadine.³⁹ Four additional patients responded within several days to haloperidol 1–3 mg.³³ In a retrospective analysis of 100 SC patients, haloperidol was successfully used in 82 out of 87 and was ineffective in five; the latter were subsequently treated with prednisone.³¹ Of the remaining 13 subjects, one was successfully treated with chlorpromazine and treatment could not be determined by case review in 12.

Pimozide (2 mg twice a day) was reported successful in a total of five patients.^{35,37} A retrospective review of patients in Turkey compared results between haloperidol and pimozide and reported that haloperidol had a significantly faster average onset of symptomatic improvement (haloperidol 14 days vs. pimozide 29 days); average time to becoming symptom free (haloperidol 42 days vs. pimozide 109 days); lower treatment failure rate (haloperidol ineffective in three vs. pimozide in five) but a greater number of drug withdrawals because of side effects (haloperidol 3 vs. pimozide 1).²⁰ This study is, however, difficult to interpret because the authors provided the initial treatment choice in 65 patients but were only able to gather adequate data in 29 patients, and failed to identify the specific treatment within this group. Side effects leading to haloperidol withdrawal included dystonia, parkinsonism, sleepiness, and cognitive issues and for pimozide, sleepiness, headache, dry mouth, and numbness. Tardive dyskinesia was not reported in any reviewed study.

Haloperidol and pimozide are described as successful agents in some case series focusing on other aspects of SC and as a failed primary therapy in published reports describing alternative agents. Data from these studies were incorporated into our total number, recognizing that negative case reports usually go unpublished and the deficiency of placebo-controlled trials. Thus, taking all evaluated studies into consideration, the results are as follows: for haloperidol, 133 out of 159 patients were successfully treated solely with this medication;^{10,20,25,31,33–35,39,40,42,44} treatment was ineffective in 119,^{10,19,20,25,31,35,48,52,55} and was discontinued because of side effects in seven.^{10,19,20} Of note, these numbers do not include 20 patients treated with either haloperidol or haloperidol plus IVIG (discussed later),⁵⁰ since it was difficult to incorporate the results of this dual therapy trial into a discussion of haloperidol efficacy. Similarly, the

Table 1. Symptomatic Treatments

Drug and Dose	Number of patients	Age of Patients (years)	Chorea Duration Before treatment	Study Design	Assessment Tool	Outcome	Adverse Reactions	Study
HLP vs. PMZ, dosage unknown	29 followed (unclear distribution)	6–17	2 d–11 y	Retrospective comparison	Qualitative	Response HLP 14.5 d PMZ 29.5 d Remission HLP 43 d PMZ 110 d	HLP: dystonia, Parkinsonism, sleepiness, forgetfulness PMZ: headache sleepiness, dry mouth, numbness	Demirenen et al. ²⁰
HLP 2–4 mg/d	2	5–12	3–6 w	Case report	Qualitative	Response in 48 h	None	Axley ³⁹
HLP 1–3 mg/d	4	8–15	2 w–8 y	Case series	Qualitative	Response in 3–4 d	None	Shenker et al. ³³
PMZ 2 mg bid	1	14	2 y	Case report	Qualitative	Response in 2 d	None	Harries-Jones and Gibson ³⁷
PMZ 2 mg bid	2	12–16	2 w–6 m	Case report	Qualitative	Response “immediate” Remission 2 w	None	Shannon and Ferniche ³⁵
CLP? dose	91	Unclear	Unclear	Retrospective comparison	Unclear	unclear	Parkinsonism	Teixiera et al. ⁶¹
HLP: 0.5–15 mg/d	HLP 82, HLP+ PR 5, CLP 1, unknown 12	2–36	4 d–8 y	Retrospective case series	Qualitative	82/87 response HLP 5/5 response specifically HLP +PR	Not reported	Tumas et al. ³¹
OLZ 5–10 mg/d	6	5–13	8–10 w	Case series	Qualitative	Remission 2–3 w	None	Sethi et al. ⁴⁶
VPA 250 mg bid	1	19	2 months	Case report	Qualitative	Response 1 d Remission 1 m	None	Mclauchlan ²²
VPA 15–25 mg/kg/d	5	11–18	5 d–2.5 y	Case series	Qualitative	Remission 5–10 d	None	Dhaneraj et al. ²¹
VPA 20 mg/kg/d	1	8	3 w	Case report	Qualitative	Response 12 h	None	Alvarez and Novac ¹⁹
VPA 15–25 mg/kg/d	15	5–13	1–104 w	Case series	Qualitative	Response 4–8 d in 13/15 pts	Severe hypotonia	Daoud et al. ³⁶

Table 1. Continued

Drug and Dose	Number of patients	Age of Patients (years)	Chorea Duration Before treatment	Study Design	Assessment Tool	Outcome	Adverse Reactions	Study
VPA 20–25 mg/kg/d	9	11	Unknown	Case series	Qualitative	Response 11 d	None	Davutoglu et al. ³⁰
VPA 20 mg/kg/d	10	9	2 w–1 y	Case series	Blinded observer	Response 3–7 d Remission 1–2 w	None	Sabui and Pant ²³
VPA 25 mg/kg/d	1	15	3 m	Case report	Qualitative	No response after 3 w	None	Appleton and Jan ³⁴
VPA 600–800 mg/d	2	12–12	2–4 d	Case report	Qualitative	Response 4–7 d Remission 12 d	None	Steinberg et al. ⁴⁵
CBZ 4–10 mg/kg/d	10	7–16	7 d–8 m	Prospective case series	Qualitative	Response, 2–14 d Remission 2–4 w	Pruritic rash	Harel et al. ²⁴
CBZ 15–20 mg/kg/d	2	8–8	10 d–3 m	Case report	Qualitative	Response 1 w Remission 1–2 m	None	Roig et al. ⁴⁴
CBZ 15–20 mg/kg/d, HLP 3 mg/d, VPA 20 mg/kg/d	HLP 6, VPA 6, CBZ 6	7–15	4 d–8 y	Comparison study	Qualitative	Response 6/6 VPA, 5/6 CBZ, 3/6 HLP	HLP: somnolence, dystonic reaction	Peña et al. ²⁵
CBZ 15 mg/kg/d, VPA 20–25 mg/kg/d	CBZ 17, VPA 7	5–14	2 d–6 m	Comparison study	Qualitative	Response CBZ 4–14 d, VPA 2–30 d Remission CBZ 3–20 w, VPA 1–25 w	None	Genç et al. ²⁶

Abbreviations: bid, Twice a Day; CBZ, Carbamazepine; CLP, Chlorpromazine; d, Days; HLP, Haloperidol; m, Months; OLZ, Olanzapine; PMZ, Pimozide; PR, Prednisone; pts, Patients; VPA, Valproic Acid; w, Weeks.

total excluded data from the previously discussed Turkish study which failed to provide the final number of patients successfully treated with haloperidol.²⁰ Pimozide was successfully used in at least six out of 17 patients,^{10,35,37} plus an unclear number of additional patients in one study discussed above.²⁰ It was ineffective in 10,^{10,20,48} and discontinued because of side effects in one.²⁰

Chlorpromazine using an ill-defined dose was successful in 10 out of 12 patients.^{20,35,42,44} In one study, five out of 91 patients developed Parkinsonism; however, no additional information was available about the effectiveness of chlorpromazine in the other 86 subjects.⁶¹ Olanzapine (5–10 mg/day) was successfully used in six patients with improvement seen in 2 days and remission of symptoms in 2–3 weeks.⁴⁶ Similar agents, such as risperidone (dose 1–2 mg twice a day), have been recommended by some authors⁶² in an effort to decrease the likelihood of extrapyramidal side effects. A lack of reports, however, limits the ability to assess their efficacy compared with other agents. Risperidone is mentioned as a failed treatment in a study focusing on plasmapheresis (discussed below).²⁹ In addition to antipsychotic medications, other agents that act on the dopaminergic system have been utilized to treat chorea in SC. Tetrabenazine, which inhibits the uptake of monoamines and causes the depletion of monoamine storage,⁶³ is approved for the treatment of chorea in Huntington's disease. A 1977 case report suggested that tetrabenazine administered to two patients with SC (25 twice a day or three times a day), is an effective chorea therapy in SC.³⁸ Symptomatic improvement was observed in 24 hours and resolution of symptoms occurred in 2 weeks. Other reports describe tetrabenazine failure in a single patient³⁷ and side effects including quadriparesis and dysarthria that resolved with its withdrawal.⁴⁰

It has been suggested that patients with SC may be particularly vulnerable to extrapyramidal side effects. For example, several studies noted above described treatment-limiting side effects with the use of haloperidol.^{19,20,31} Support for increased neuroleptic side-effect susceptibility in SC also comes from a comparison of five out of 91 cases with SC who developed significant extrapyramidal side effects on chlorpromazine as compared to 10 age-matched patients with Tourette's syndrome (TS) receiving equivalent medication doses.⁶¹ Unfortunately, this protocol controlled for age but not gender, and four of the five patients in the SC group were female, compared with only two out of 10 TS controls. Thus, it is unclear whether this sensitivity is unique to SC or reflects a gender difference. An additional study reported that 19 out of 32 SC patients had motor symptom side effects secondary to the use of other medications that affect the dopaminergic system, including decongestants, stimulants, and antiemetics, but no control group was provided.⁶⁴

Antiepileptic medications. Given the reported side effects of dopamine antagonists, alternative symptomatic treatments have been sought. Two case reports found that valproic acid (20 mg/kg/day or 250 mg twice a day) was effective in two SC patients who had previously failed either haloperidol or diazepam.^{19,22} Ten patients responded to valproic acid (20 mg/kg/day) as a secondary treatment, although the

specific agents trialed before valproic acid are not specified.²³ A slightly higher dose of 300 mg twice a day was used successfully in a case of chorea paralytica.⁴¹ An additional three case series containing a total of 26 patients reported successful treatment with valproic acid (20–25 mg/kg or 600–800 mg/day) as initial therapy in 24 out of 26 patients.^{30,36,45} For all studies reviewed in which valproic acid was prescribed, it was reported to be effective in a total of 64 out of 78 patients,^{10,19,21–23,25,26,30,35,36,41,42,45,46} and ineffective in 14 patients.^{10,29,34,36,48,52,53} There are no reports of side effects including sedation, vertigo, or liver failure. One patient had severe hypotonia, although this did not recur when the drug was reintroduced.³⁶ Where reported, symptomatic response occurred between 12 hours and 10 days, and complete remission of symptoms occurred in 1–4 weeks, except in the case of chorea paralytica, where remission was reported within 14 months. Of note, time to response was not reported in this patient.

Carbamazepine is also reported to be effective. In one case report two patients with SC treated with carbamazepine (15–20 mg/kg) had improvement 1 week after therapy initiation, and complete remission in 1–2 months.⁴⁴ Another report evaluated nine patients treated with carbamazepine (4–10 mg/kg) prospectively as first line therapy.²⁴ Chorea improved in 2–14 days and complete remission occurred in 2–12 weeks. A pruritic rash was the only side effect reported and did not limit treatment. A small comparison study randomized 18 SC patients to treatment with either carbamazepine, valproic acid, or haloperidol.²⁵ A good clinical response was noted in six out of six patients treated with valproic acid (20 mg/kg/day); five out of six treated with carbamazepine (15–20 mg/kg/day); and in three out of six treated with haloperidol (3 mg/kg/day). Of note, no statistical analysis of efficacy was performed and there was no placebo control group. The authors did, however, describe a good clinical response to valproate in the four patients who failed initial treatment with either haloperidol or carbamazepine. A third study showed no significant difference in time to symptomatic improvement, duration of improvement, or side effects between carbamazepine (15 mg/kg; n=17) and valproic acid (20 mg/kg; n=7) groups.²⁶ In the total reviewed literature, carbamazepine was reported to be effective in 33 out of 34 patients^{24–26,31} and ineffective in one.²⁵

In terms of other antiepileptic medications, levetiracetam has been mentioned as an attractive option because of its favorable side effect profile. To date, however, despite its prescription in other choreiform disorders, there is only a single case report of its successful use in SC.⁵⁵ No other reports, positive or negative, were identified specifically for levetiracetam. Phenobarbital is rarely used today because of sedation and other side effects, but it has been reported to be effective in at least 13 SC cases.⁴² Similarly diazepam is reported as effective in at least three out of four patients in older reports, but rarely in reports after 2000.^{35,42}

Immunomodulatory treatment

Steroids. Given that Sydenham's chorea is proposed to be an autoimmune disorder, immunomodulatory treatments have also been utilized (Table 2); steroids being the most frequently reported therapy.

Table 2. Immunosuppressive Treatments

Drug and Dose	Number of patients	Age of Patients (years)	Chorea Duration Before treatment	Study Design	Assessment Tool	Outcome	Adverse Reactions	Study
PR × 2 mg/kg/day × 3 w with taper	5	4–11	2–30 d	Case series	Qualitative	Response 24–48 h remission 7–12 d	None	Barash et al. ³²
CR IV 30–40 u/d × 3–9 d, taper PR 30–75 mg/d for 5–10 d, taper	8	6–10	2 w–7 m	Retrospective case series	Qualitative	Response in 3–5 d	None	Green ²⁷
MP IV 25 mg/kg/d × 5 d DF 0.9 mg/kg/d × 3 m	10	7–11	15 d	Prospective case series	USGRS	Response 48 h, Remission 21 d	None	Fusco et al. ⁵³
MP IV 25 mg/kg/d (children) or 1 g/d (adults) × 5 d, PR taper	5	11–46	Not specified	Case series	Unique 4-point scale	Response 5 d	Cushing's syndrome	Cardoso et al. ⁵⁶
MP IV 25 mg/kg/day × 5 d, 1 mg/kg PR taper	5	4–12	4–8 w	Case series	USGRS	Chorea subscale decreased from mean of 14 to mean 8 at 1 month	Weight gain, moon face	Teixeira et al. ⁵⁶
PR 2 mg/kg/d × 4 w 25 day taper	22 PR, 15 placebo	7–11	2–84 d	Prospective double blind randomized control trial	Chorea intensity scale	Significant difference in weekly score	Weight gain, moon face	Paz et al. ⁴⁹
IVIG 400 mg/kg × 5 d	2	11–13	2–2 m	Case report	Qualitative	Remission “several” days	None	van Immerzeel et al. ²⁸
2 g/kg IVIG	1	10	14 d	Case report	Qualitative	Response 4 d	None	Boresma et al. ⁵²
2 g/kg IVIG	1	13	1 w	Case report	USGRS	UCSRS 45 onset, 18 3 weeks, 2 at 3 months	None	Mohammad et al. ⁵⁴

Table 2. Continued

Drug and Dose	Number of patients	Age of Patients (years)	Chorea Duration Before treatment	Study Design	Assessment Tool	Outcome	Adverse Reactions	Study
HLP 0.025–0.05 mg/kg/d ± 1 g/kg IVIG × 2 days	10 HLP, 10 IVIG+HLP	5–13	7–140 d	Open label randomized comparison study	Unique 16 point scale	HLP +IVIG improved scores at 1,3 and 6 months	None	Walker et al. ⁶⁷
PLEX × 5 d	1	16	Not specified	Case report	Unspecified	Response 1 m	None	Miranda et al. ²⁹
IVIG 1 g/kg/d × 2 d, PLEX × 5 days PR 1 mg/kg × 10 d	4 IVIG, 8 PLEX 6 PR	5–14	Not specified	Open label randomized comparison	Mean Chorea Severity Scale	Response in all (no clear statistical difference)	PR: weight gain, moon face	Garvey et al. ⁵¹

Abbreviations: CR, Corticotropin; d, Days; DF, Deflacort; h, Hours; IVIG, Intravenous Immunoglobulin; m, Month; MP, Methylprednisolone; PLEX, Plasmapheresis; PR, Prednisone; USGRS, Universidade Federal de Minas Gerais Sydenham's Chorea Rating Scale; w, Weeks.

Prednisone (1 mg/kg orally for 5 days with gradual taper) was successfully used to treat chorea in five patients who had previously failed therapy with haloperidol.³¹ Initial therapy with prednisone (2 mg/kg for 3 weeks with a 3 week taper) was successful in five patients, with a clinical response in 24–48 hours, and total remission in 7–12 days.³² A double-blind randomized control trial compared 22 patients treated with oral prednisone (2 mg/kg/day for 4 weeks with a 25-day taper) with 15 patients treated with placebo.⁴⁹ Clinical response was noted in 1 week in the prednisone group and 2 weeks in the placebo group. Complete remission was achieved by 54 days in the prednisone group and 120 days in the placebo group. The authors concluded that steroids significantly decreased chorea intensity and the time to remission, although relapse rates were the same in both groups. As noted by others,⁶² however, significant limitations of this study include the use of a non-validated chorea rating scale and failure to control for the simultaneous use of haloperidol in both the prednisone (n=4) and placebo (n=7) groups. Further, statistically significant visibly detectable side effects, including weight gain (2.3 kg in the prednisone group versus 0.5 kg in placebo group at 8 weeks), and a cushingoid appearance in the prednisone group, may have compromised observer blinding. Other steroid treatment studies include eight patients who received corticotrophin (30–40 mg intravenously for 3–9 days), followed by prednisone (30–75 mg for 5–10 days), and a 90-day taper.²⁷ A total of 20 patients in three additional studies were treated with intravenous methylprednisolone (25 mg/kg/day or 1 g/day in adults) for 5 days followed by either a prednisone taper (1 mg/kg/day oral prednisone; n=10)^{48,56} or deflacort (0.9 mg/kg/day; n=10).⁵³ Of note, 14 of these patients had chorea paralytica.^{53,56} In these three studies, steroids represented either the initial treatment (n=5) or treatment following a failure to respond to pimozide, haloperidol, valproic acid, or chlorpromazine (n=15). Clinical response was noted in 2–5 days, after the initiation of steroid therapy. Reviewing all available literature, combining both IV and oral steroid treatment, and recognizing variability in agents, dosing, and administration route, steroid therapy was successful in 76 out of 77 patients.^{10,27,29,31,32,36,43,48,49,51,53,56} Only one failure of steroid treatment was reported.²⁹ Two patients overall developed Cushing's syndrome⁴⁸ and a transient weight gain with moon facies was reported in an additional patient.⁵⁶ In two other studies (total n=28),^{49,51} a weight gain and moon face was reported, but the number of individuals with these side effects was not provided.

IVIG. Case reports utilizing IVIG include a total of four patients who improved following the receipt of IVIG (a total of 2 gm/kg) over 5 days.^{28,52,54} One subject had failed valproic acid and haloperidol prior to treatment with IVIG, whereas the others were treated with IVIG as a primary therapy. Therapeutic improvement was reported in 4 days in one out of four patients; improvement time for the others was not clearly specified. A previously mentioned small comparison study evaluated 10 children treated with haloperidol alone versus 10 children with haloperidol plus IVIG (total of 2 gm/kg) administered over 2 days.⁵⁰ Based on ratings by a blinded observer, there was a statistically significant improvement in the haloperidol + IVIG group at 1, 3, and

6 months of treatment and a reduced duration of haloperidol treatment compared with those receiving only haloperidol. Concerns for this study include lack of placebo control arm, use of a non-validated rating scale, and failure of the blinded observer to perform the initial evaluation at the beginning of the protocol. In a follow-up of these patients, it has been suggested that there might be a difference in executive function at 1, 3, and 6 months between those subjects treated with IVIG + haloperidol compared with haloperidol alone.⁶⁵ Statistical analyses included a comparison to a “healthy” control group, rather than a simple comparison of the original cohorts. In summary 18 out of 18 patients appeared to respond to IVIG, including an additional comparison study of IVIG, plasmapheresis and steroids (discussed below). No reports of clear IVIG failure have been published nor have publications described side effects.

Plasmapheresis. In a single individual case report, five rounds of plasmapheresis were successfully used to treat a patient with SC who had previously failed valproic acid, risperidone, and IV steroids/per os (PO) taper.²⁹ A comparison study evaluating results in patients who received IVIG (n=4), plasmapheresis (n=8), or oral prednisone (n=6), showed no significant differences between groups.⁵¹ The authors did, however, note that the chorea severity score was variably reduced in the different treatment groups at 1 month: IVIG 72%, plasmapheresis 50%; oral prednisone 29%. Based on this finding it was suggested that IVIG therapy might lead to a quicker recovery. Limitations of this study include the small number of subjects, the lack of a placebo arm, use of a non-validated rating scale, and the fact that study participants were also receiving a variety of symptomatic treatments (valproic acid, haloperidol, benzodiazepines). No side effects were reported in published studies.

Other treatments. A single case report suggested improvement of symptoms in four patients with SC because of the administration of vitamin E (50 IU) administered daily for 2 weeks.⁴⁷ No other literature was identified evaluating this treatment.

Discussion

“A point of view can be a dangerous luxury substituted for insight and understanding” Marshall McLuhan

The goal of this review was to critically analyze the available literature on the treatment of chorea in individuals with SC. To achieve this goal, available case reports, case series, and treatment trials were reviewed. Although it was previously recognized that data were limited, it was enlightening to recognize the significant deficit of valid scientific evidence for all reported therapies. Most available therapeutic information exists in case reports, case series, or small comparative series, and only a single study was placebo controlled. Further complicating therapeutic decision-making is the fact that the sole placebo-controlled study reported improvement of chorea after 2 weeks of placebo treatment.⁴⁹ Hence, based on this information, it becomes more difficult to assert that the reported success of a therapeutic agent represents its beneficial action or merely a therapeutic tincture of time. In addition, studies vary on when and how clinical

assessments were performed, whether treatment was primary or secondary, and how long symptoms had been present before treatment was initiated. While the relative rarity of SC and its natural clinical variation is recognized, larger, better-controlled studies, using a uniform standard and a validated rating scale, are required before definitive therapeutic recommendations can be presented. Future studies utilizing the USCRS to assess the response to therapy are required and not just highly desirable. Placebo-controlled trials would be ideal, but are difficult to justify.

All symptomatic treatment of chorea in SC is based on the off-label use of medications in small case series or comparison studies, none of which are placebo controlled. Given that chorea typically resolves spontaneously over time, in very mild cases, pharmacotherapy may be unnecessary. This non-therapeutic approach was successfully utilized in 12 of 65 patients in one case series.²⁰ Clearly, in patients with more significant symptoms, therapy is recommended. Evidence is insufficient, however, to strongly recommend one drug over another.

Pathophysiologically, chorea has been associated with neurotransmitter alterations within basal ganglia circuits, either excessive dopaminergic transmission, or a lack of gamma-aminobutyric acid (GABA)ergic (inhibitory) or acetylcholinergic activity.⁶⁶ As described, several antidopaminergic agents have been reported to be effective in treating chorea. The available literature supports a beneficial response to haloperidol; however, it is the neuroleptic most reported to cause unacceptable side effects. On the basis of the available information, pimozide, which has fewer side effects, may be less effective. Chlorpromazine may be effective, but detailed information on dosing and efficacy is lacking. Atypical antipsychotics, such as risperidone and olanzapine, are favored by some authors, but again there is little evidence supporting their use.

Several AEDs alter GABAergic neurotransmission making them potential candidates for the treatment of chorea. Medications such as valproic acid and carbamazepine, are attractive choices based on their low side effect profile and preliminary suggestive data that they may be as effective as haloperidol.

Immunomodulatory therapies for the treatment of chorea in SC remain controversial primarily due to their invasive nature and potential side effects. Recognizing that some studies suggest that recurrent episodes of SC may not be immune mediated,^{7,59} future studies of immunomodulatory therapies should attempt to correlate outcomes with measurements of proposed biomarkers. Accumulating evidence does support a beneficial effect of steroids. Prior recommendations in the literature have suggested reserving this approach for patients with severe chorea including chorea paralytica, those unresponsive to symptomatic therapies, or individuals with unacceptable side effects. Steroids have been used as first-choice therapy in chorea paralytica, although there is also a single case report of successful treatment using valproic acid. Of note, immunosuppression with steroids should be utilized with particular caution in areas where diseases such as tuberculosis are endemic.⁶⁷ Other immunomodulatory therapies such as IVIG and plasmapheresis have been tried in a small number of patients, but remain relatively untested.

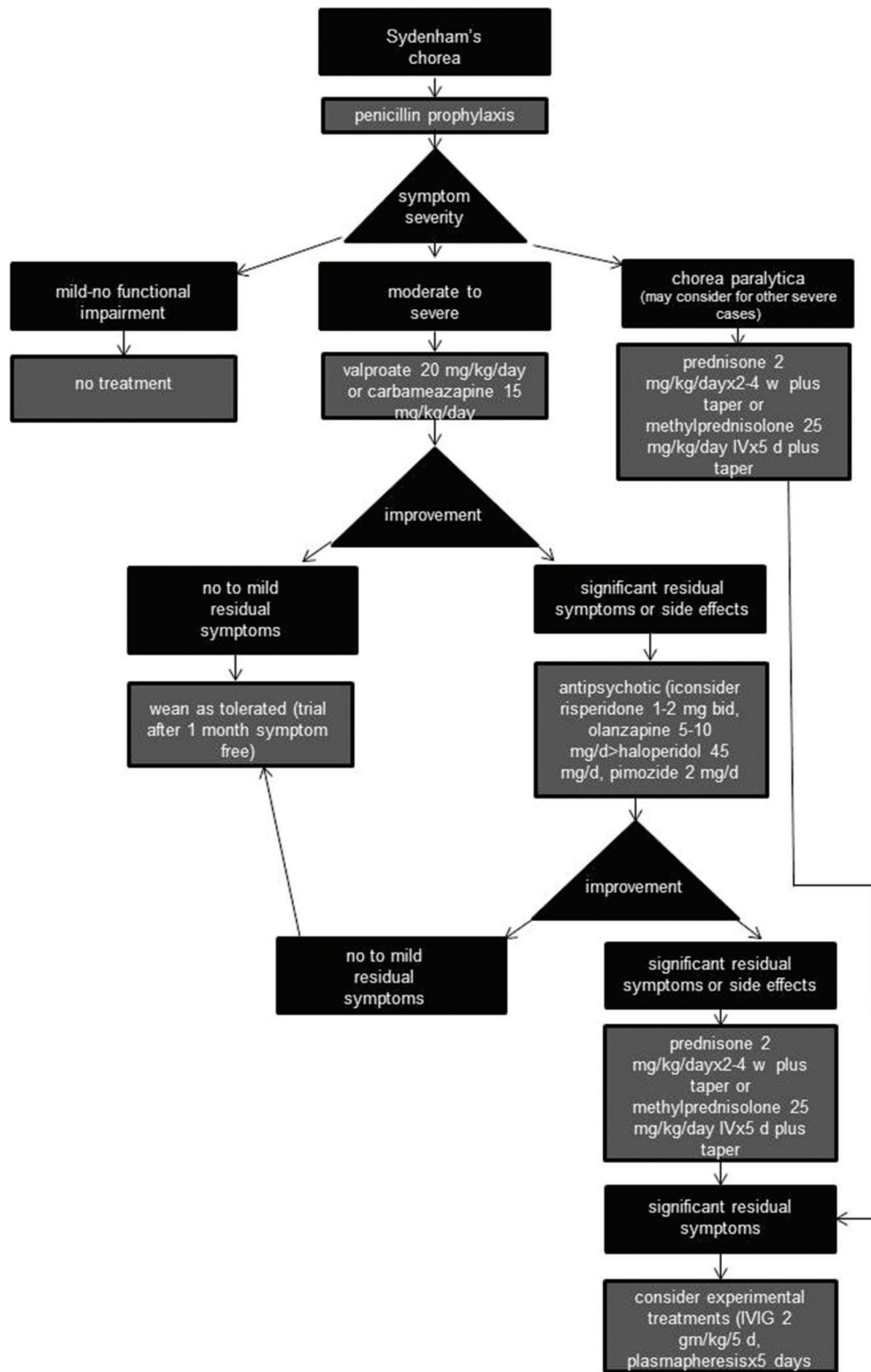


Figure 1. Treatment Recommendations. Our suggested approach to treatment is presented.

Conclusions

When considering a therapeutic agent for the treatment of chorea in individuals with SC, the practitioner should consider the severity of the problem, the requirement for a therapeutic agent, its availability, cost to the family, extent of supporting evidence, and the therapy's side effect profile. Given that the literature does not clearly demonstrate one treatment being clearly superior, a practitioner's personal experience and comfort with a given agent will likely guide their ultimate therapeutic choices. Based upon our review of the literature, a suggested potential therapeutic pathway for the treatment of chorea in SC is presented in Figure 1. Based upon the number of successful reports and their favorable side-effect profiles, we favor the initial use of valproic acid (20 mg/kg/day) or carbamazepine (15 mg/kg/day). As they have more significant side effects and there is a lack of evidence that they are more effective, neuroleptics should be reserved for patients who fail valproic acid or carbamazepine therapy. We concur with others that there is evidence to support a role for immunomodulatory therapy. Nevertheless, we believe that it should be reserved for patients with chorea paralytica or for those with disabling symptoms who fail, or cannot tolerate, symptomatic treatment. Of the immunomodulatory therapies investigated, steroids have the strongest supporting evidence, but side effects are not uncommon. Oral prednisone (2 mg/kg/day) for 3–4 weeks with prolonged taper and methylprednisolone (25 mg/kg/day) with a prolonged taper are the two most commonly utilized regimens. Although there is a theoretical basis for IVIG and plasmapheresis and it appears to have at least equal efficacy in a single small comparison study, we hesitate to recommend these approaches before a trial with steroids. In conclusion, the preparation of this manuscript has enlightened us to the acute need for well-controlled studies to assist in clarifying the most appropriate therapy for the treatment of chorea in Sydenham's chorea.

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