Post Streptococcal Syndromes, A Rheumatologist Perspective
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Abstract
Post streptococcal syndromes may manifest in multiple organs including the musculoskeletal, central nervous, urinary, integumentary, and circulatory systems. The commonly described post streptococcal syndromes include acute rheumatic fever, post streptococcal glomerulonephritis, post streptococcal arthritis, and pediatric autoimmune neuropsychiatric disorders. Classically, these complications occur more often in children. While much is written in the pediatric literature regarding these syndromes, a compilation of information is difficult to find. This article summarizes some of the frequently described post streptococcal syndromes and associations.

DESCRIPTION OF STREPTOCOCCUS
Group A beta-hemolytic streptococci (GAS), Streptococcus pyogenes, the most extensively studied member of the streptococcal family is a gram-positive cocci that appears in chains and pairs and demonstrates beta hemolysis (full lysis) on blood agar. Five to fifteen percent of the general population harbor this bacterium in the upper respiratory tract without disease. Nonetheless, GAS maybe responsible for numerous infections and infection related syndromes.(Table 1).

PATHOPHYSIOLOGY
Streptococcus is classified based on antigen serology (Lancefield groups) to certain polysaccharides in the bacterium cell wall. GAS has an extensive array of virulent factors (Table 2). M proteins, virulent factors found on the cell surface oppose phagocytosis. Over 50 antigenically distinct M proteins are associated with GAS. M proteins often divide into rheumatogenic and nephritogenic.
serotypes. Serotypes 5, 6, and 19 relate to human heart tissue and serotypes of 1, 12, and 49 relate to renal tissue. Some serotypes are associated with both arthritis and renal syndromes.

**Figure 2**

### EPIDEMIOLOGY

The global burden of severe GAS disease is estimated to be greater than 500,000 deaths a year, primarily from rheumatic heart disease. The estimated prevalence of severe GAS disease (e.g., acute rheumatic fever, rheumatic heart disease, post-streptococcal glomerulonephritis, and invasive infections) is 18 million cases. Superficial GAS diseases such as pyoderma and pharyngitis also contribute to disease burden. Some countries in Indo Pacific and Middle Eastern regions report symptomatic pharyngitis 5-10 times that of other more developed countries.

In the United States, approximately 8,950-11,500 cases of invasive GAS disease occur each year, with 1,050-1,850 deaths. Toxic shock syndrome and necrotizing fasciitis each represent about 6%-7% of these cases. However, several million cases of strep throat and impetigo are reported each year.

**IMMUNE MEDIATED THEORY**

The suspected relationship of streptococcal disease and post-streptococcal immune mediated sequelae is expanding, but making such an association between an infection and a post infectious syndrome requires certain criteria (Table 3). Several immune mechanisms may be operable in post streptococcal syndromes such as antibody directed molecular mimicry in rheumatic fever, and possible super antigen stimulation of T cells in Kawasaki disease and guttate psoriasis.

**EVALUATION FOR STREPTOCOCCUS**

Antistreptolysin O (ASO) and anti DNAse B antibodies are the most consistently studied streptococcal antibodies. Prior data suggested that individually, anti DNAse B or ASO have 70% sensitivity 86-93% and specificity. The combined elevation of both (ASO and anti DNAse B) revealed a sensitivity of 95% and specificity of 98%. A more recent study reports single point antibody titers are unreliable and GAS infection assessment may require a correlation with increasing antibody titers.

Post streptococcal syndromes usually occur 1-3 weeks after pharyngitis or skin infection. Some syndromes may occur within a few days of infection, making antibody confirmation of disease difficult. Therefore reexamining titers after several weeks is important. Other syndromes (movement and neuropsychological) may be occult and occur months after the inciting infection.

**POST STREPTOCOCCAL SYNDROMES**

**ACUTE RHEUMATIC FEVER (ARF)**

**OVERVIEW**

Rheumatic fever is a multisystem nonsuppurative complication of GAS infections. Most patients present several weeks after streptococcal pharyngitis or scarlet fever, but in others no identifiable infection is found. Over twenty million children world wide experience rheumatic fever and up to 4% relate to untreated streptococcal infections. In the United States outbreaks of ARF have steadily declined over the past 80 years and the disease is relatively uncommon. Most outbreaks occur in developing countries in areas plagued by impoverished overcrowded conditions with limited access to antibiotic therapy. The worldwide estimates of ARF are up to 471,000 cases per year, with the highest rates in aboriginal populations and New Zealand.

**CLINICAL FEATURES**

Migratory polyarthritis or arthritis generally involves the lower joints but can migrate to the upper extremities. This occurs early in the disease often the earliest complaint. Up to
17% of patients present with a mono-arthritis usually involving the knee. Small pea size painless subcutaneous nodules of extensor surfaces are seen in less than 10% of patients. This is frequently seen in association with carditis. Carditis may manifest as pericarditis, myocarditis or endocarditis. The mitral valve is almost always affected although any valve can be involved. Mitral stenosis and calcification are common manifestations of long standing rheumatic heart disease. Rheumatic heart disease post ARF may be as high as 60%. Erythema marginatum, primarily involves the trunk, consisting of evanescent erythematous rings that spares the face. Sydenhams chorea is a late manifestation (discussed in more detail later), and typically occurs weeks to months after the streptococcal infection.

**DIAGNOSIS**

The Jones criteria (Table 4), was established to make a presumptive diagnosis of ARF. Two major, or one major and two minor criteria, along with evidence of recent or current streptococcal infection as documented by throat culture, increasing ASO or anti DNAse B, are considered sufficient to make the diagnosis.

**IMMUNOPATHOLOGY**

The most compelling etiopathogenic theory in rheumatic fever and heart disease suggests antibodies to N-acetyl glucosamine of the streptococcus demonstrate cross reactivity with human laminin and myosin. These antibodies may also contribute to the infiltration of T cells, triggering the release of cytokines contributing to inflammation and granuloma formation (aschoff bodies) of the sub endocardium leading to valve scarring. Genetic links including HLA-DRB1*07 and HLA-DR*16 have been reported with ARF and rheumatic heart disease.

**TREATMENT**

Treatment includes non-steroidal anti-inflammatory drugs (NSAIDs) for arthritis and appropriate antibiotics therapy {penicillin or erythromycin for penicillin allergy}. A recent streptococcal pharyngitis meta-analysis has shown that the cephalosporin cure rate may be superior to
penicillin. Antibiotic prophylaxis is suggested for patients with persistent valvular heart disease for at least 10 years after the last episode of acute rheumatic fever or until 40 years of age, whichever is longer. In patients without persistent valvular disease, prophylaxis is recommended to continue for 10 years or until the patient is 21 years of age, whichever is longer.

**OVERVIEW**

Post streptococcus reactive arthritis is an acute nonsuppurative arthritis following a known streptococcal infection. It was first described in 1959 by Crea and Mortimer as “Scarlatinal arthritis”, later described by Goldsmith et al in children who failed to meet criteria for ARF. Classically, this follows pharyngitis by 3-14 days. Over 80% of PSRA are GAS affiliated, but it can be seen with group B, C, and G infections, as well. Peak incidence is often bimodal, in ages 8-14 years and 21-37 years.

**CLINICAL FEATURES**

Proposed criteria for the diagnosis includes evidence of prior strep infection, a non migratory arthritis, recurrent or protracted arthritis and arthritis not highly responsive to NSAIDs. It can manifest in any joint including axial joints in 24% of cases.

**DIAGNOSIS/TREATMENT**

PSRA is treated with NSAIDs tapered off as the arthritis improves. Patients may require several months of treatment. All patients should be treated for streptococcus infection as well. Because of the quick onset of arthritis, the initial ASO and anti DNAse B titers may not be elevated. Titers should be repeated a few weeks post infection. Some consider PSRA a variant of ARF supported by the finding that about 6% of patients have silent carditis found on echocardiograms usually 6 months after the onset of arthritis. The American Heart Association suggest antibiotic prophylaxis for at least one year, and if carditis is not observed prophylaxis can then be discontinued.

**POST STREPTOCOCCAL RELATED MYALGIA/MYOSITIS**

Myalgias are reported in association with streptococcal and/or post streptococcal syndromes. Clinical presentations include severe muscle pain and/or tenderness. Laboratory data may show elevation in sedimentation rates and leukocytosis, but muscle enzymes and muscle biopsies may be normal. Several cases of post streptococcal polymyalgias have responded to penicillin, NSAIDs or steroid therapy. Orbital myositis has been reported to respond to antibiotic and anti-inflammatory therapies.

**POST STREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)**

PSGN is nephritis with or without oliguric renal failure, and occurs one to three weeks after pharyngitis or skin disease. An estimated 470,000 cases of PSGN occur per year accounting for 5000 deaths annually. The majority of deaths occur in developing countries.

**CLINICAL FEATURES**

Patients can present with peri-orbital edema, hematuria (tea, dark, coke colored urine), hypertension, malaise, weakness and back pain. Children may have a mild subclinical course.

**IMMUNOPATHOLOGY MECHANISM**

The immune mechanisms for PSGN are unclear, but immune complex disease, is likely. IgG and C3 immune deposits are present in the mesangial basement membrane with increased cellularity and evidence of endothelium proliferation. Other proposed mechanisms include cross reactive antibodies and exotoxins. SpeB (Strep exotoxins B) has been identified in biopsies, but its role is unclear. Nordstrad et al has speculated SpeB may induce massive cytokine production and by cleavage mechanisms cause the release of M proteins, C5α peptidase and other surface bound streptococcal antigens. Some of the nephritogenic M type products may inhibit complement function, including SIC (Streptococcal inhibitor of complement), CRS (Closely related to SIC) and DRS (Distantly related to SIC).

**DIAGNOSIS/TREATMENT**

Most patients have mild, non-progressive disease and are not biopsied. Typically a low serum C3 and mild renal insufficiency are seen. Occasionally progression to chronic renal failure occurs. Ongoing streptococcal infections should be treated. However, most patients are treated supportively.

**POST STREPTOCOCCAL CNS SYNDROMES**

Post streptococcal CNS syndromes are difficult to categorize. Syndromes may overlap and the symptoms may be remote from the inciting infection. The following syndromes or manifestation have been reported or proposed.
SYNDEHAMS CHOREA (SC)

SC was first described in the 17th century although its association with streptococci and rheumatic fever was not noted until the late 1800’s. Not until 1950 was the association made with GAS. SC usually manifests weeks to months after a streptococcal infection, although occasionally within one week. Typically, chorea is bilateral, uncontrolled purposeless, rapid movement of the limbs with associated emotional lability. Chorea is a major criterion of ARF and thought to be a result of cross reactive antibodies to brain tissue. T and B cells may participate in CNS surveillance under “normal conditions,” and these lymphocytes potentially recognize self antigens, release cytokines and chemokines, and recruit more inflammatory cells. This may suggest a loss of tolerance of auto reactive T and B cells perhaps due to streptococcal antigen.

Most episodes are monophasic, but up to 42% relapse. These relapses may be related to streptococci or other infectious triggers. SC manifestations are variable lasting for several months to years. Tics, attention deficit hyperactive disorder (ADHD), depression and obsessive-compulsive disorder (OCD) have been described in association with synodehams chorea. In one report a family history of rheumatic fever and/or SC was seen in up to 36% of patients.

PANDAS

Pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS) is a group of neurological sequeale that includes chorea, tics, obsessive compulsive behavior, ADHD, depression, anxiety and oppositional defiant behaviors (ODB). Making a temporal relationship of PANDAS with streptococcal infection has been controversial. Some studies have demonstrated patients with PANDAS have increased serum levels of antineuronal antibodies. The proposed criterion for PANDAS is inexact and non-discriminating (Table 5). Two clinically distinct phenotypes have been defined; movement disorders (Tics, chorea and dystonia) and psychiatric disorder (OCD, ADHD, anxiety, depression and oppositional defiant behaviors). An additional classification scheme suggests central nervous hyperkinetic syndromes (movement, insomnia and anxiety) or hypo-kinetic syndromes (depression and hyper-somnolence).

Figure 5

Table 5

<table>
<thead>
<tr>
<th>Proposed criteria for PANDAS</th>
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<tr>
<td>1. OCD or tics</td>
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<td>2. Per-puberty onset</td>
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<td>3. Episode is abrupt</td>
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<td>4. Associated with group A streptococi</td>
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<td>5. Associated with sensor abnormalities and adventitious movements ADHD or chorea.</td>
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MOVEMENT DISORDERS ASSOCIATED WITH PANDAS

1. TICS

Tics are sudden, repetitive, stereotyped motor movements or phonic productions. The concept of post-streptococcal tics was first described in 1980 with an outbreak of tonsillitis in Rhode Island when there was a 10 fold increase in cases of tics. Tics may recur or worsen with recurrent streptococcal infections.

2. MYOCLONUS AND DYSTONIA

Myoclonus is brief involuntary muscle twitching and dystonia is sustained muscle contractions with twisting, repetitive movements or abnormal postures. Myoclonus and dystonia have been associated with post streptococcal disease and both have been described with and without Parkinson features. Occasionally a Parkinson phenotype is associated with hyperkinetic and/or hypo kinetic syndromes.

3. SYNDEHAMS CHOREA-SEE PRIOR DISCUSSION.

BEHAVIORAL/PSYCHIATRIC DISORDERS ASSOCIATED WITH PANDAS

OCD AND ADHD

Psychiatric and behavioral manifestations are common. Streptococcal infections may precede OCD symptoms by months. There is some suggestion that ADHD may predate the development of post streptococcal movement disorders.

ENCEPHALITIS LETHARGICA (EL)

EL was first described in the early 1900’s (perhaps the precursor for the PANDAS syndrome) with symptoms of headache, malaise, fatigue, insomnia and ophthalmologic manifestations. EL has associated insidious movement and/or psychiatric disorders including Parkinson’s, oculogyric crisis, chorea, myoclonus, mutism, catatonia, and behavioral problems such as anxiety, depression, and
EL can occur in a wide age range from 2-69, most cases reported in children or teenagers. Dale and colleagues described CSF findings of elevated protein and oligoclonal bands in EL patients. Magnetic resonance imaging (MRI) demonstrated inflammatory changes on T2 weighted images in 40% of these patients. Sixty-five percent of these patients also had elevated ASO titers.

CNS VASCULITIS
CNS vasculitis has been reported in conjunction with PSGN. One case report described vasogenic edematous changes on MRI imaging and Doppler stenosis of both extra and intra cranial vessels. CNS vasculitis patients generally presented with seizures and cognitive dysfunction. Most improve with steroid treatment.

DIAGNOSIS CNS SYNDROMES
Assessing for anti-neuronal antibodies in the CSF and serum has produced inconsistent results between different antineuronal assays. Currently, it is not routinely recommended to test for anti-neuronal antibodies in the clinical setting.

Most post streptococcal CNS syndromes have normal neuroimaging. However, nonspecific MRI abnormalities are reported in some.

TREATMENT CNS SYNDROMES
Antibiotics for infection and prophylaxis are important especially if there is evidence of syndehams chorea or rheumatic fever. A prospective study suggested antibiotic treatment of tonsillitis showed improvement in OCD manifestations. A double blinded randomized control trial suggested a reduction in the incidence of post streptococcal CNS manifestations with the use of prophylactic antibiotics. In a review article by Dale, he cited several articles that suggested that PANDAS syndromes may respond to steroids, plasma exchange, IVIG, however, no current recommendations for treatment with these agents is has been suggested at this time.

POST STREPTOCOCCAL SYSTEMIC VASCULITIS
HENOCH–SCHÖNLEIN PURPURA (HSP)
Henoch–Schönlein purpura is an IgA mediated small vessel vasculitis and is the most common vasculitis in children. The incidence is approximately 10-20/100,000. HSP is usually preceded by an upper respiratory infection (including streptococcal infections) and may manifest with palpable purpura, arthralgia/arthritis, abdominal pain (due to vasculitis and intussusception in some), or renal disease. Renal findings include hematuria and proteinuria associated with mesangial involvement. Incomplete HSP presentations occur.

Patients with streptococcal associated HSP may have a low C3 and elevated ASO titers. One case control study reported elevated ASO titers associated with a tenfold increase risk for HSP compared to patients with negative titers. Nephritis-associated plasmin receptor (NAPtr), a GAS antigen, has been reported in glomerular biopsies of patients. Renal disease is usually limited and the prognosis is good, although occasionally patients develop progressive renal failure with nephrotic syndrome. Treatment for progressive renal disease includes steroids and cytotoxic agents. Renal disease, if associated with streptococci, may respond to antibiotics.

The arthritis associated with HSP; primarily involves the lower extremity large joints. It often responds to NSAID therapy.

POLYARTERITIS NODOSA (PAN)
Polyarteritis nodosa is a small and medium vessel vasculitis, usually seen in middle age men. In children it tends to be a disease of pre-teen males. It can occur in the systemic form with multiple organ involvement or in the cutaneous form (discussed later). Symptoms include constitutional manifestations, muscle pain, arthritis, abdominal discomfort and abnormal urinalysis. While cutaneous PAN has been associated with streptococci, only a few cases of the systemic form have been reported post streptococcal.

KAWASAKI’S DISEASE (KD)
Kawasaki’s disease a multisystem medium vasculitis commonly affecting children is characterized by prolonged fever, conjunctivitis, erythema (especially of the extremities and trunk), inflamed oral mucosa, cracked lips, strawberry tongue, desquamating rash of distal extremities (fingers and toes), and cervical adenopathy.

Streptococcal and staphylococcal superantigens and/or infections have been suspected in the pathology. Over the past three decades a single microbial cause has not consistently been identified. Several theories postulate the connection of KD and streptococcal infections, these include streptococcal antigen as an inciting factor causing clonal T cell expansion and may stimulate T cells with specific TCR V[beta] types. Researchers have suggested...
staphylococcal enterotoxin A (SEA), SEB, SEC, toxic shock syndrome toxin-1 (TSST-1), and streptococcal pyrogenic exotoxin A (SPEA) may be involved in the pathogenesis based on documented elevations of IgM antibodies to these antigens in KD patients.

The initial treatment of KD may include antibiotics because of a suspected bacterial infection, but the standard treatment of KD includes IVIG and aspirin in the early acute febrile phase. Re-treatment may be indicated if the patient is no better within 36 hours of the initial IVIG infusion. In refractory cases of KD, some have considered steroids, plasma exchange, cyclosporine and possibly biologics; however, lack of controlled data makes treatment recommendations with these agents unclear.

POST STREPTOCOCCAL DERMATOLOGIC MANIFESTATIONS

Overview

Infection and colonization’s of skin with bacteria may lead to inflammatory skin disease. Toxins from streptococcal and staphylococcal may act as allergic superantigens.

CUTANEOUS POLYARTERITIS NODOSA (CPAN)

CPAN is a pan arteritis of the subcutaneous and deep dermal arterioles, post capillary venules, without systemic involvement. Painful small (0.5-2 cm in diameter) nodules that may ulcerate are typical. Patients may have elevated sedimentation rates, fever, arthralgias, myalgias, leukocytosis or leukopenia. The etiology is unknown. Fibrinoid degeneration of the elastic lamina of small and medium vessels with findings of fibrin, C3 and IgM deposits are seen on excisional biopsies of skin nodules. An association with viral hepatitis infections is described in the literature and there are reports of post streptococcal infection association.

CPAN may relapse with recurrent streptococcal infections. In these cases long term treatment with antibiotics may be necessary, in some immunosuppression may be required. A case report of a 13 year old presenting with polyarthritis, myalgias, elevated ASO titers and biopsy findings of necrotizing vasculitis, showed improvement with prednisone and penicillin. Disease recurrences was noted with penicillin withdrawal. Another case report implicated dental carries and abscesses as a source of streptococcal related CPAN. Extraction of teeth and abscess drainage resolved the vasculitis.

PUSTULAR VASCULITIS (PV)

PV is generally classified as a neutrophilic dermatosis. It was first described by Strutten et al in 1995. Large purple purpuric based blisters and pustules on the dorsum of the hands, laterally between digits (especially between the thumb and index) and on the soles of the feet are classic. PV is usually treated with prednisone. An association with streptococcus, including elevations of ASO, has been reported. In such patients antibiotic treatment may be indicated.

ERYTHEMA ELEVATUM DIUTINUM (EED)

EED are red edematous purpuric plaques on the extensor surfaces of the body. A leukocytoclastic vasculitis with fibrinoid necrosis is the primary histopathology. An allergic reaction to streptococcal superantigens as suggested in one case report. Dapsone is usually the treatment of choice.

POST STREPTOCOCCAL PUSTULOSIS (PAG)

PAG is a rare condition manifesting as small pustules on normal skin in the acral location. It is associated with fever, arthropathy, leukocytosis, elevated sedimentation rates and in some, elevated ASO titers. The histological findings include sub corneal spongiform pustules within normal epidermis and progression to leukocytoclastic vasculitis. PAG may occur in the first few weeks after streptococcal infection. It is commonly treated with antibiotics and steroids.

PANNICULITIS AND ERYTHEMA NODOSA (EN)

Panniculitis is a group of disorders characterized by inflammation of subcutaneous adipose tissue. EN, a subtype of panniculitis, (septal panniculitis) is considered the most common form of panniculitis seen in children. Raised painful subcutaneous erythematous nodules on the lower extremities, buttock and dependent areas are typical. Fatigue, weight loss, joint pain, infections, drugs, chronic inflammatory disease and malignancy may be associated.

Streptococcal infection is the most common identifiable cause in children. However, the peak age of onset is 20-30, with females outnumbering males. In most patients, a prodrome of upper respiratory infection and/or evidence of a prior streptococcal pharyngitis are seen. Because, EN occur 2-3 weeks after streptococcal infections, obtaining
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throat cultures, ASO and Anti DNase B titers at presentation is important. Pathological evidence suggests that EN is related to type IV hypersensitive reaction to a variety of antigens.\textsuperscript{117} Septal inflammation with neutrophilic infiltrate around proliferating capillaries with occasional hemorrhage, and small well defined nodular aggregates of histiocytes around a central stellate is seen.\textsuperscript{108,117} Lesions may take weeks to months to resolve. Along with treating the underlying triggers; NSAIDs and occasionally steroids may be required. For those with associated streptococcal infections treatment should include antibiotics.\textsuperscript{117}

**PSORIASIS**

Psoriatic lesions are red, raised, often scaly and found primarily on the extensor surfaces, scalp, trunk and the periumbilical area. Reports have described streptococcal microbial products affecting the lesional epidemics of psoriasis patients.\textsuperscript{119} Streptococcal M proteins and skin keratins share some homology suggesting a pathologic role for cross reactivity.\textsuperscript{120} A recent prospective trial of 248 patients revealed patients with chronic psoriasis reported sore throats ten times more often than controls.\textsuperscript{121} GAS was isolated in 10% of patients and only 1% of control.\textsuperscript{127}

**GUTTATE PSORIASIS (GP)**

Guttate psoriasis is characterized by sudden onset of diffuse red scaly papules that often resolve spontaneously but at times progress to chronic plaque psoriasis.\textsuperscript{122} The etiology is unknown. Genetic and environmental factors and possibly GAS may be involved.\textsuperscript{123,124,122} The onset of occurs 1-2 weeks after an episode of tonsillitis or pharyngitis.\textsuperscript{123} Studies demonstrating streptococci isolation from the throats of GP patients have shown that some isolates have the ability to produce streptococcal pyrogenic exotoxin C (SPEC) and superantigens known to stimulate certain V beta T cells regions.\textsuperscript{125} Some have suggested that streptococcal infections may induce GP through superantigen driven generation of V beta-restricted (cutaneous lymphocyte associated antigen) CLA-positive skin homing lymphocytes.\textsuperscript{16}

**CHRONIC PLAQUE PSORIASIS (CPP)**

CPP is the most common form of psoriasis characterized by erythematous plaques with silvery scales. The association of GAS, chronic psoriasis or psoriasis vulgaris remains largely anecdotal.\textsuperscript{121} There are reports of exacerbations of psoriasis in patients with tonsillitis and reports of significant remission rates after tonsillectomy and/or antibiotic treatment.\textsuperscript{126-129} A recent meta analysis did not show benefits for cross reactivity. A recent meta analysis did not show benefits.\textsuperscript{122} Currently no specific recommendations can be made regarding these treatments.\textsuperscript{130}

**CONCLUSION**

In summary, post streptococcal syndromes and associations are often multi system. Clinicians should remember that most post streptococcal syndromes occur weeks to months after the initial infection. Searching for a previous history or evidence of streptococcal infection is important. Multisystem manifestations often suggest autoimmune diseases but the differential should include streptococcal related syndromes.

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