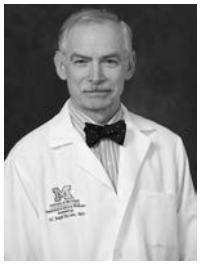
Editorial introduction

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editor for this issue.

SECTION EDITOR

W Joseph McCune



Dr W Joseph McCune MD is Michael and Marcia Klein Professor of Rheumatic Diseases and Director of the Lupus Program at the University of Michigan. Following an Internal Medicine residency at the University of Michigan and a fellowship in Immunology and Rheumatology at Harvard Medical School and the Brigham and Woman's Hospital, Dr McCune has been a member of the faculty at the University of Michigan where he specializes in the epidemiology, diagnosis, and treatment of lupus and systemic vasculitis.

Should CAR-T cells be used as monotherapy?

William Joseph McCune

During the past century, new therapies for rheumatic diseases have been introduced that promised to dramatically alter the disease course with the hope, usually unfounded, that long-term disease control without other, supplementary therapies could be achieved. The dramatically successful introduction of dehydrocorticosterone for rheumatoid arthritis garnered the Nobel Prize for Phillip Hench and his colleagues despite the fact that the original recipient became disabled and embittered by corticosteroid complications (Matteson, personal communication) which in time were widely recognized in other patients after long term use. Only after corticosteroids were used sparingly in combination with other therapies was optimal benefit obtained [1]. Similarly, the introduction of monthly intravenous cyclophosphamide was followed by demonstration that a six-month course was inadequate to maintain remission and most patients, and that following induction of by this relatively toxic agent long term maintenance with better tolerated compounds achieves the best result.

The futility of assuming that even the most 'heroic' therapies for severe lupus can reliably produce a durable remission without additional treatment is illustrated by the long-term outcome of two aggressive treatment regimens, total lymphoid irradiation and autologous stem cell transplantation.

Total lymphoid irradiation for severe lupus was administered at Stanford from 1980 to 1987, Lupus patients with diffuse membranoproliferative glomerulonephritis were treated with total lymphoid irradiation in combination with a tapering dose of prednisone and with discontinuation of immunosuppressive drugs. Dramatic initial improvement was reported; at follow up of the initial 10 patients' proteinuria improved in all, and 80% had improvement of their glomerular filtration rate [2]. Following treatment lupus serologies also improved and corticosteroids were withdrawn in most patients [3]. Renal biopsies at short term follow-up showed dramatically reduced disease activity although there was some progression of scarring [4].

In contrast, the results after long term follow-up of 21 patients over an average of 10.7 years were not favorable. Genovese reported 'Fifteen of twenty-one patients (71%) remained alive at the time of this assessment. Nine of the 21 patients (43%) survived without developing end-stage renal disease (ESRD). The probability of long-term survival without ESRD and without need for additional immunosuppressive agents after total lymphoid irradiation was 19%' [5]. Hence, despite initial clinical and serological improvement and virtual absence of biopsy evidence of active nephritis the improvement was not reliably durable.

Stem cell-based strategies have included autologous stem cell transplantation, a short-lived trial of high dose cyclophosphamide and allogeneic stem cell transplantation. Of these autologous stem cell transplantation has been most frequently performed. In the United states Burt *et al.* reported the results of autologous hematopoietic stem cell transplantation for patients with severe lupus who had been refractory to multiple therapies, an average of 6.5 immunosuppressive drugs, including subjects with nephritis, cerebritis, and antiphospholipid syndrome [6,7]. Initial results were highly favorable with a 90% remission rate At follow-up reported remission rates were of 71% at 3 years, and 50–62% at 5 years with 85% survival In the European Group for Blood and Marrow Transplantation Registry, 28 patients with refractory disease received autologous stem cell transplantation [8]. After 5 years, the survival rate was 80% and disease flare free survival was only 30%. The authors suggested that the outcome was satisfactory for most in part because either cyclosporine or MMF administered prospectively after transplantation resulted in less severe flares

We come now to the question of whether chimeric antigen receptor T-cell (CAR-T) cell s should be used as monotherapy. In the above examples impressive short-term responses to aggressive therapy did not predict a durable response without further treatment. Despite its impressive efficacy

Michael and Marcia Klein Professor of Rheumatic Diseases, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to William Joseph McCune, MD, Michael and Marcia Klein Professor of Rheumatic Diseases, University of Michigan, Ann Arbor, MI, USA.
E-mail: jmccune@med.umich.edu

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of CAR-T cell therapy over 2-3 years, can we be confident that long term outcomes after 5-10 years of CAR-T cell treatment (or newer related therapies developed to avoid the burden of harvesting and treating allogeneic cells) will not show some loss of efficacy? Initial studies have shown that dramatic clinical responses accompanied by elimination of most pathogenic autoantibodies are followed by gradual albeit partial reconstitution of immune [9]. In this setting, it is reasonable to ask if, following an p period of time to enable B cell depletion, it might be particularly reasonable to consider adding hydroxychloroquine compound that has been shown both to preserve disease remission and prevent emergence of new disease manifestations such as nephritis, without increasing the risk of infection [10,11].

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Conflicts of interest

There are no conflicts of interest.

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Management of cutaneous manifestations of systemic sclerosis: current approaches and emerging therapies

Rocio Bautista Sanchez[a], *Yasmin Khader*[a] *and Dinesh Khanna*[a,b]

Purpose of review
This review summarizes the most recent approaches in managing cutaneous involvement, one of the main clinical manifestations of systemic sclerosis (SSc). The following article is written for clinicians and researchers looking for optimizing patient care and exploring new therapies.

Recent findings
Recent studies have shown advancements in the management of cutaneous manifestations of SSc. While mycophenolate remains the first-line treatment, other immunosuppressive therapies targeting different pathways have shown promising results. B-cell depleting agents, such as Rituximab (RTX), are being increasingly utilized for cutaneous scleroderma with positive outcomes. Intravenous immunoglobulins (IVIG) have also demonstrated potential benefit for refractory cases with advanced skin fibrosis.
Moreover, emerging approaches such as autologous hematopoietic stem cell transplant (AHSCT) have been evaluated in clinical trials, with evidence suggesting its ability to reset the immune system and achieve remission in skin involvement in severe cases. Chimeric antigen receptor (CAR) T cell therapy is the most recent potential pathway to target refractory skin and systemic disease.

Summary
Management of cutaneous involvement in SSc remains challenging. The following study provides a comprehensive review of the most recent updates in treating cutaneous aspects (and associated complications) of SSc to help clinicians establish a more effective approach managing this condition.

Keywords
cutaneous scleroderma, immunosuppression, management, skin fibrosis, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disorder characterized by vasculopathy and fibrosis which affects the skin and internal organs [1]. Skin involvement is a hallmark feature that affects 95% of patients with SSc. It ranges from puffy fingers to skin hardening and thickening that vary in extent and severity. The extent of skin involvement divides SSc into its limited and diffuse cutaneous subtypes (Table 1). This classification helps determine the disease course with potential organ involvement, prognosis, and subsequently guides the treatment plan

PATHOPHYSIOLOGY OF CUTANEOUS SYSTEMIC SCLEROSIS

The pathophysiology of cutaneous SSc involves complex interplay between immune dysregulation, vascular involvement and fibrosis. Initial injury in the endothelium leads to endothelial dysfunction, likely driven by the immune activation. Recent data suggest that cytotoxic T lymphocytes in the skin are primarily driving the endothelial injury, apoptosis, and downstream activation of pro-fibrotic cytokines in early untreated patients with SSc [2]. Using systems biology (single cell RNA sequencing), there is robust interplay between the endothelial cells (with potential to transition into mesenchymal cells) and

[a]Division of Rheumatology, Department of Medicine and [b]University of Michigan Scleroderma Program, University of Michigan, Ann Arbor, MI, USA

Correspondence to Dinesh Khanna, MD, MSc, Professor of Medicine, Frederick G. L. Huetwell Professor of Rheumatology, Director, University of Michigan Scleroderma Program Division of Rheumatology/Department of Internal Medicine, Suite 7C27, 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109, USA. E-mail: khannad@med.umich.edu

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KEY POINTS

- Systemic sclerosis associated skin and musculoskeletal involvement often result in long-term disability that can be attenuated with medical and occupational therapy.
- Immunosuppressive should be considered in patients with early progressive diffuse cutaneous systemic sclerosis.
- Advanced cellular therapies (e.g. CAR-T cell therapy) are a novel emerging therapy that has provided promising results in recent case series.
- Hematopoietic stem cell transplant is highly effective for the treatment of advanced or refractory cases of systemic sclerosis but requires careful patient selection.

myofibroblasts, both contributing to the extracellular matrix deposition and drive pro-fibrotic signaling [3▪▪]. Early SSc skin involvement has a high prevalence of innate and adaptive immune signatures, whereas later skin tissue shows marked hyalinized collagen with little evidence of immune activation. In a US cohort, SSc patients with mean disease duration of 1.3 years had a high prevalence of M2 (96%) and M1 (94%) macrophage and CD8 T cell (65%), CD4 T cell (60%), and B cell (69%) signatures [4]. More details about pathogenesis of early skin fibrosis are published in a recent reviews [5].

Autoantibody formation

Antinuclear antibodies (ANAs) are the most prevalent antibodies, occurring in approximately 95% of cases. The presence of ANA, along with SSc-autoantibodies and nailfold capillaroscopy abnormalities in patients with Raynaud's phenomenon, is highly predictive of developing SSc.

Scleroderma-specific antibodies include anticentromere antibodies that have been associated with limited cutaneous systemic sclerosis (lcSSc). On the other hand, antitopoisomerase I antibodies (ATA) are strongly correlated with diffuse cutaneous systemic sclerosis (dcSSc), small and large joint contractures, and early digital ulceration. RNA polymerase antibodies have also been shown to be associated with accelerated skin progression with relationship with scleroderma renal crisis and significant small and large joint contractures [6].

CLINICAL PRESENTATION

The cutaneous manifestations of SSc are variable and significantly affect disease severity and prognosis (Fig. 1). Skin thickening is the hallmark of SSc and can present as sclerodactyly, which is thickening and hardening of the skin that is limited to the fingers, lcSSc, and dcSSc [7▪].

Raynaud's phenomenon is one of the earliest and most prevalent manifestation of scleroderma. It is typically caused by loss of vasodilatory capacity within the digital arteries leading to vascular spasms in response to cold or stress. Additionally, endothelial dysfunction along with impaired fibrinolysis and activation of coagulation pathways play an important role in the pathogenesis of Raynaud's [8]. Chronic and/or severe Raynaud's can lead to digital ulceration, pitting scars, and gangrene in severe cases, significantly affecting the quality of life.

Other cutaneous manifestations may include telangiectasias, which are small, dilated blood vessels typically seen on the hands, face, and mucous

Table 1. Cutaneous scleroderma subtypes and their associated key features

Subtype	Key features
Limited cutaneous systemic sclerosis	Skin involvement: Limited to the face, distal aspects of limbs - upper extremities up to the arms, and lower extremities up to the knees Raynaud's phenomenon: Usually present for many years before the other symptoms Associated organ involvement: High risk (10–15%) of pulmonary hypertension, skin calcinosis, gastrointestinal involvement, and telangiectasias Renal involvement: Rarely affected Antibodies: Anticentromere antibody (ACA) positive in 50–60% of cases, while anti PM/Scl and anti-Scl-70 present in 5–10%
Diffuse cutaneous systemic sclerosis	Skin involvement: Involves distal and proximal aspects of the body, including upper arms, thighs, and torso Raynaud's phenomenon: Typically starts within one year of non-Raynaud's signs and symptoms, shortly before or followed by skin thickening Puffy fingers are the most common first non-Raynaud's sign or symptom Associated organ involvement: Higher risk of interstitial lung disease, renal disease, and myocardial involvement Antibodies: Anti-Scl-70 antibodies are positive in 15-30%, and anti- RNA-polymerase III antibodies in 15-30% of cases and varies based on geographic distribution

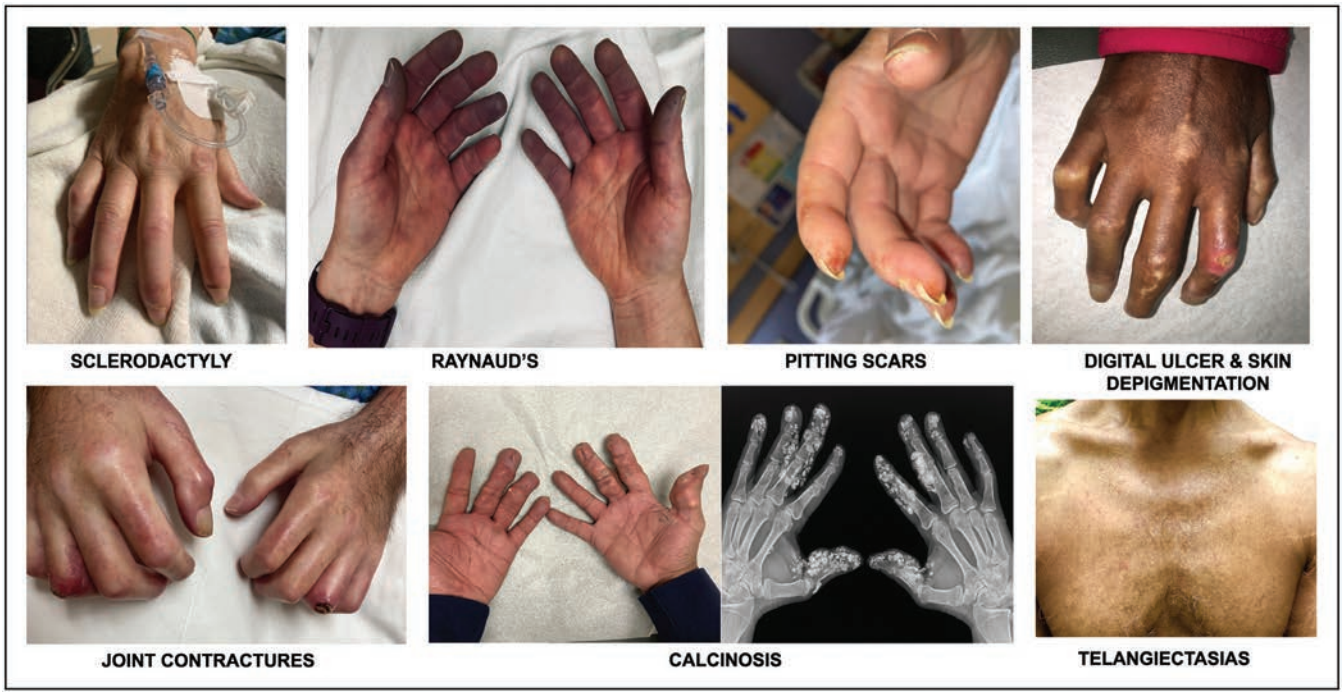

FIGURE 1. Cutaneous and musculoskeletal manifestations of systemic sclerosis .

membranes. Calcinosis is another manifestation of cutaneous scleroderma resulting from calcium salts deposits on the skin that can ulcerate and become infected. Additionally, traumatic ulcers are painful sores that can develop over the bone prominences as a result from skin breakdown and are associated with significant morbidity. Skin depigmentation, which gives the characteristic 'salt and pepper' appearance of the skin, results from melanocyte damage impairing their pigmentation pattern. Pruritus is another common feature caused by skin damage, inflammation, and vascular changes leading to itching and discomfort. Allodynia, which is characterized by skin sensitivity (feeling of sunburn), is often associated with nerve fiber damage and impaired innervation to the skin due to inflammation and fibrosis [9].

Joint contractures (both small and large joint involvement) can also result from severe skin thickening and fibrosis, leading to restricted joint mobility.

Fig. 1 shows pictures of different cutaneous manifestations of SSc.

MANAGEMENT OVERVIEW

The main goal of management of cutaneous manifestations of SSc is to minimize inflammation/immune deregulation, reduce the progression of skin fibrosis, prevent or reduce complications like digital ulcers and joint contractures, and subsequently improve the hand function and quality of life. It is a dual approach that balances immunosuppressive (disease-modifying) therapies to treat the underlying inflammation/ fibrosis axis and symptom control to address patient's concerns. Fig. 2 highlights the approach to cutaneous manifestations and Fig. 3 outlines the initial management approach for cutaneous SSc based on their initial symptoms and the duration of those symptoms.

A PRACTICAL APPROACH TO SKIN THICKENING

Localized scleroderma: phototherapy and laser therapy

Topical corticosteroids and topical tacrolimus have been historically prescribed by dermatologists for the treatment of localized areas of skin thickening [10]. Ultraviolet A1 (UVA-1) phototherapy applied to skin models of patients with scleroderma show upregulation of antifibrotic pathways and downregulation of pro-fibrotic pathways (e.g., TGF-ß) [11–13]. There are published studies showing efficacy in localized scleroderma of Psoralen + ultraviolet A (PUVA) with the greatest efficacy in early inflammatory lesions while UVA-1 excels in sclerotic skin lesions [14]. There are case reports in SSc where UVA1 treatment has been successful. However, many patients with SSc are treated with

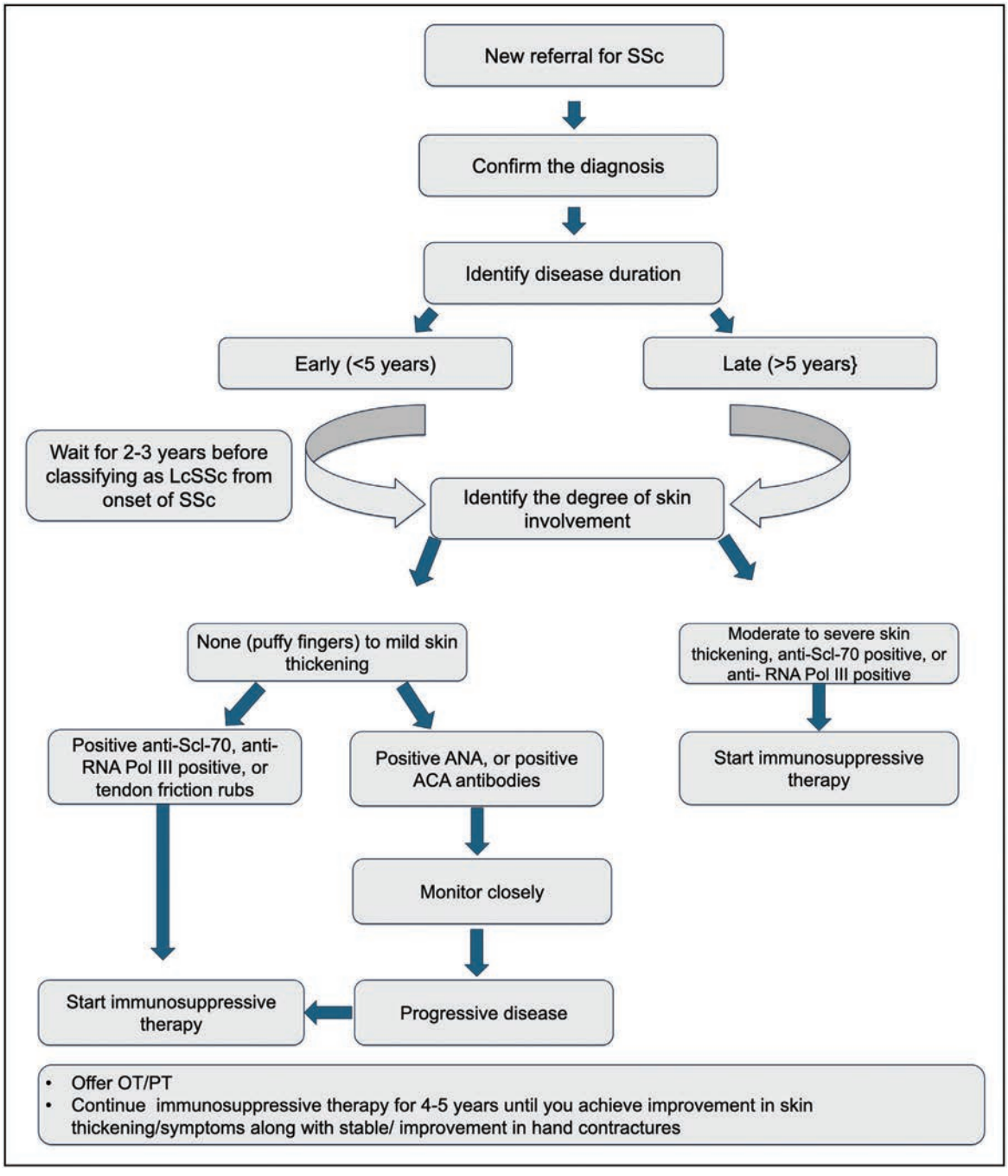

FIGURE 2. Summary of how to approach patients with cutaneous scleroderma. ACA, anti-centromere antibodies; ANA, antinuclear antibodies; lcSSc, limited cutaneous systemic sclerosis; OT, occupational therapy; PT, physical therapy; SSc, systemic sclerosis.

immunosuppressive therapy, due to systemic nature of the disease, and not with UVA1 treatment.

Fractional ablative carbon dioxide laser (FAL) has been used to decrease skin fibrosis and improve skin elasticity in patients with morphea. FAL has been reported to be effective in observational studies and to be superior to low dose UVA-1 phototherapy in one clinical trial, although it is not widely utilized in United States [15,16]. FAL has also been evaluated with and without the use of topical methotrexate (MTX) [17]. Lastly, an open-label RCT utilized pulsed dye laser for the treatment of telangiectasias in the head and neck with favorable results [18▪]. Patients should be referred to dermatology for phototherapy or laser therapy evaluation when feasible. Immunosuppressive therapies, as described below,

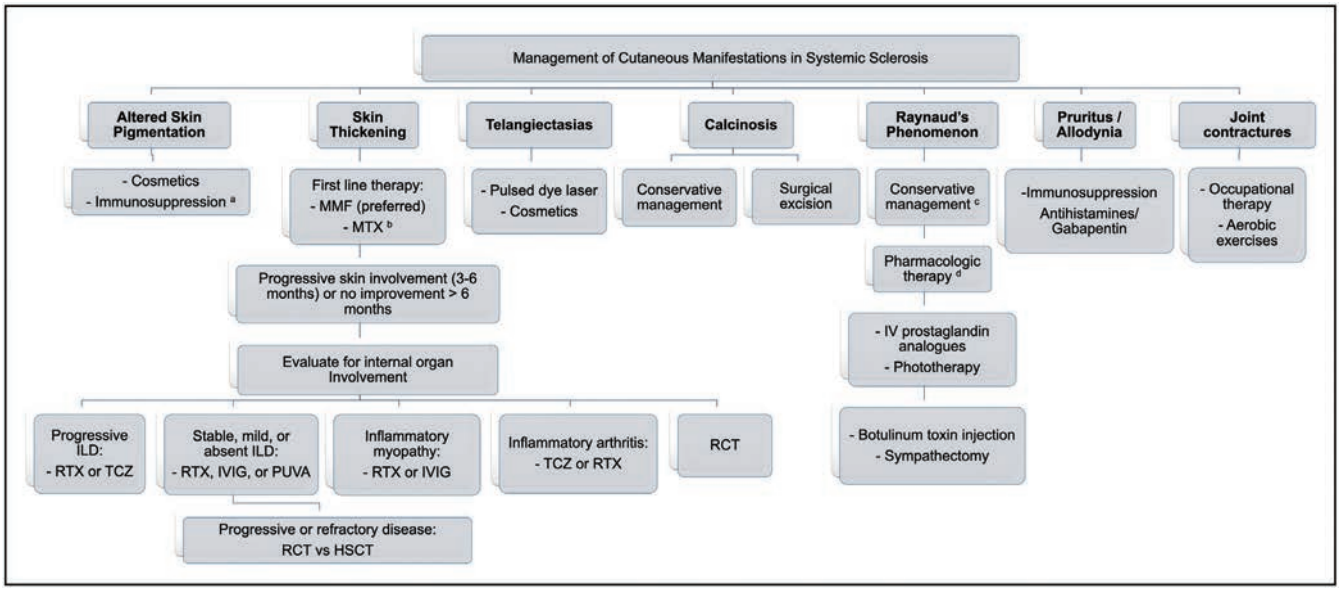

FIGURE 3. Suggested treatment algorithm for cutaneous manifestations of systemic sclerosis. A. Assure the patients that pigmentation changes will improve with compliance over the years. B. Preferred in the absence of ILD and presence of inflammatory arthritis. C. Avoiding cold objects and weather, wearing gloves with hand warmers, abstaining from smoking, stopping drugs that promote vasoconstriction. D. Calcium channel blockers, phosphodiesterase-5 inhibitors, endothelin-1 receptor antagonists. HSCT, hematopoietic stem cell transplant; ILD, interstitial lung disease; IV, intravenous.IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; MTX, methotrexate; RCT, randomized clinical trial; RTX, rituximab; TCZ, tocilizumab.

are prescribed for large, involved areas with significant disability, and/or deep morphea (morphea profunda).

In our practice, in conjunction with our dermatologists, we prescribe topical corticosteroids and tacrolimus for the treatment of local lesions. In addition, for those who have widespread disease or treatment resistant disease we prescribe UVA therapy for at least 3 to 6 months to see a beneficial effect. Patients should be referred to dermatology for phototherapy or laser therapy evaluation when feasible.

Early diffuse skin thickening: mycophenolate mofetil versus methotrexate

The immunomodulatory therapies that are discussed below have shown benefit on the treatment of other manifestations of SSc and can be considered for skin and musculoskeletal involvement in patients with SSc.

The two most used therapies for early and progressive skin thickening in patients with SSc are methotrexate (MTX) and mycophenolate mofetil (MMF).

MMF is commonly used for the treatment of SSc. The active metabolite of MMF is mycophenolic acid, which reversibly impairs lymphocyte proliferation and can modulate fibroblast biology [19]. Different case series and secondary analyses from the Scleroderma Lung Study (SLS) II showed that MMF was beneficial in improving skin involvement, as assessed by the modified Rodnan skin score and most utilized therapy in the US for early SSc with progressive skin involvement [20].

MTX is known to act as a competitive inhibitor of the enzyme dihydrofolate reductase, leading to a reduction of folinic acid levels and pyrimidine synthesis [21]. At low doses, MTX has shown to increase intracellular and extracellular levels of adenosine, which modifies the activity of immune cells and fibroblasts [22]. Two small randomized clinical trials (RCTs) studied the use of MTX in SSc [23,24]. The largest study included 71 patients with dcSSc and less than 3 years of diagnosis with skin involvement. At 12 months, mRSS was -4.3 in the MTX group versus (vs) 1.8 in the placebo group ($P < 0.009$) [23]. Both trials used lower doses of MTX (15 mg weekly) compared to the higher target dose of 25 mg weekly that is now used. MTX remains a commonly prescribed medication for the treatment of skin involvement and can be considered first line in patients with concurrent inflammatory arthritis. There are also geographic variations, based on the costs and availability of these medications. In a recent international trial focused on early dcSSc, MMF was most prescribed therapy followed by MTX [25].

Beyond skin thickening: managing patients with multiorgan involvement

Rituximab

Rituximab (RTX) is chimeric mAB that targets the CD20 receptor on B cells and eradicates them [26▪]. RTX has been studied in SSc with a specific interest in the treatment of SSc-ILD [27▪,28▪▪,29]. The DESIRES trial evaluated RTX vs. placebo measuring change in mRSS as the primary endpoint. Twenty-eight patients received RTX 375 mg/m^2 weekly for 4 consecutive weeks or placebo. At 24 weeks, mRSS was significantly lower in the rituximab group than in the placebo group (−6.30 vs. 2.14; [95% CI − 11.00 to − 5.88]; $P < 0.0001$) and led to approval of RTX in Japan [30]. An open-label extension ran from week 24 to week 48 that showed improvement in mRSS for patients in the rituximab-rituximab group and in the placebo-rituximab group [31]. In an open-label trial comparing RTX vs. monthly pulse cyclophosphamide (CYC) therapy in early dcSSc and ILD, RTX was associated with a favorable impact on mRSS vs. CYC. RTX is an appropriate and effective second-line therapy for SSc patients who do not respond to MMF/MTX and also for those with underlying ILD, inflammatory arthritis, and/or inflammatory myopathy when present.

Tocilizumab

Tocilizumab (TCZ) is an anti-interleukin-6 (IL-6) receptor mAb and its use for the treatment of skin disease remains controversial. The efficacy of TCZ in patients with an early diagnosis of SSc (< 5 years) was evaluated in two multicenter, double-blinded RCTs: the phase two faSScinate and the phase three focuSSced trials. The primary endpoint was the difference in mean change from baseline in mRSS at 24 weeks in the faSScinate trial and at 48 weeks in the focuSSced trial. Neither trial met its primary endpoint, however greater numerical improvement in mRSS was observed in the TCZ group [32,33]. The clear benefits in pulmonary function tests in patients with SSc-ILD in the TCZ group lead to the FDA approval of TCZ for the treatment of SSc. TCZ can be considered as second line therapy in patients especially in those with ILD, inflammatory arthritis, and elevated inflammatory markers are present.

Intravenous immunoglobulins

Intravenous immunoglobulins (IVIGs) are an immunomodulatory therapy that has been shown to prevent skin and dermal thickening, decrease pro-inflammatory cytokine response, and reduce inflammatory skin infiltrates in experimental mice models with SSc [34]. Only one RCT has been published evaluating the difference in mRSS in SSc patients who received a single course IVIG (2 g/kg) vs. placebo and no difference was found at 12 weeks [35]. A recent large retrospective multicenter study in 78 patients with SSc found a statistically significant improvement from baseline mRSS with the use of IVIG (15 ± 12.4 to 13 ± 12.5 [$P = 0.015$]) [36]. A systematic literature review on the use of IVIG in SSc evaluated 11 studies from which eight yielded positive results favoring IVIG, especially in patient's refractory to immunosuppressive therapies [37▪]. In our practice, we utilize IVIG for progressive skin involvement where first (and sometimes second-line therapies) are ineffective, those with significant side effect profile with immunosuppressive therapies, active disease such as tendon friction rubs, and patients with inflammatory myopathy.

Stem cell transplantation

Autologous hematopoietic stem cell transplantation (AHSCT) has been studied for SSc in the ASSIST (2011), ASTIS (2014), and SCOT (2018) trials and is the most effective treatment for skin disease at present. Patients enrolled in the ASSIST and ASTIS trials received nonmyeloablative therapy plus AHSCT or intravenous (i.v.) cyclophosphamide [38,39]. At 1 year, mean mRSS went from 28 to 15 in the ASSIST AHSCT group and increased in the placebo group ($P = 0.0004$) [38]. The 2-year follow up of ASTIS trial showed mRSS change of - 19.9 in the AHSCT group vs. − 8.8 in the placebo group ($P < 0.001$) [39].

Patients in the SCOT trial received myeloablative therapy followed by AHSCT or CYC for 12 months, mRSS improved in the majority of patients in the AHSCT arm (86%) and only in 49% of patients in the CYC arm [40]. AHSCT, although very effective, is reserved for patients with severe skin disease with progressive internal organ involvement (usually ILD) and those who are refractory to immunosuppressive therapy given its significant morbidity.

Emerging therapies: a glance into the future and the role of clinical trials

There are multiple ongoing trials targeting proinflammatory and profibrotic cytokines and chemokines in SSc to stabilize and improve skin involvement that are recently published [41▪]. At our center, trials are considered as part of the treatment algorithm as no treatment is currently FDA approved for cutaneous manifestations of SSc.

In addition, cellular therapies, including chimeric antigen receptor (CAR) T-cell therapy targeting CD19, have shown preliminary but promising

data for patients with moderate to severe cutaneous and extra-cutaneous manifestations of SSc [42▪▪, 43▪▪,44]. More data are needed, including larger trials, and consideration for patients with significant skin involvement with or without ILD and internal organ involvement.

PRURITUS AND DRY SKIN

Pruritus is a bothersome and common symptom in early progressive SSc. There is neuropathic component with possible compression of small nerve fibers by thickened and/or dense collagen contributes to the pruritic skin. Conservative measures to decrease pruritus include taking showers shorter than 10 min, showering with lukewarm water, utilizing moisturizing skin lotion, and liberal frequent application of emollients. Oral antihistamines are first-line of treatment and low-dose gabapentin can be used if conservative measures fail to improve the symptoms, especially with associated allodynia. Ultimately, addressing skin thickening will be the most effective way to achieve symptom control.

JOINT CONTRACTURES

Joint contractures are common in both lcSSc and dcSSc. Small joint contractures are due to progressive skin thickening and resulting tendon shortening and usually in those who are ATA positive [45].

Other cause of joint contracture includes inflammatory arthritis. Large joint contractures are associated with dcSSc and higher mortality. Occupational and physical therapy are somewhat effective in preventing further progression, although effects wane off once therapy is stopped [46]. In 2023, EULAR released nonpharmacologic recommendations for patients with systemic lupus erythematosus and SSc and emphasized orofacial, hand, aerobic, and resistance exercises with the aim to decrease microstomia, improve hand function, and decrease disability [47▪,48].

MICROSTOMIA

Microstomia is decreased in mouth aperture due to loss of fat and fibrosis around the perioral area. Education and regular exercises may help prevent or stabilize microstomia. Immunosuppressive therapies seem to be ineffective in preventing development of microstomia. FAL and other phototherapies have shown benefits by improving limited mouth opening in patients with SSc [49]. Finally, autologous fat grafting and hyaluronidase are a promising option for patients with microstomia and microcheilia [50,51,52▪].

CALCINOSIS CUTIS

Calcinosis is commonly seen in later part of SSc. No medical treatments are widely accepted. Large or bothersome deposits can be treated with surgical excision [53,54]. Other therapies used include laser therapy, IVIG, RTX, minocycline, diltiazem, among others but provide mixed effects [55▪]. However, there is no definitive or effective therapy for this manifestation.

RAYNAUD'S PHENOMENON AND DIGITAL ULCERS

Nonpharmacological interventions for Raynaud's phenomenon such as avoiding cold objects and weather, wearing gloves with hand warmers, abstaining from smoking, or vasoconstrictive substances are the first steps in management. The appearance of digital ulcers indicates severe Raynaud's phenomenon leading to ischemia and can be treated with oral dihydropyridine calcium channel blockers or phosphodiesterase-5 inhibitors, followed by endothelin-1 receptor antagonists [56,57▪, 58,59]. If there is concern for worsening or rapid digital ischemia, the patient should be hospitalized for infectious and thrombotic investigation and prompt i.v. prostacyclin analogue administration [60]. Other strategies such as botulinum toxin injections and sympathectomy are available for refractory cases.

CONCLUSION

The cutaneous manifestations of SSc remain a common and yet complicated feature of the disease that warrant a comprehensive approach in terms of diagnosis and management. Current management is driven by symptoms and signs but lacks disease-modifying effects. Advances in immunosuppressive therapies have provided variable options to treat, stabilize, and prevent disease progression. Natural softening of skin complicates the assessment of therapeutic response of available therapies. Understanding the pathophysiology of the disease is critical for appropriate and timely management that will improve patient outcomes.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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Pediatric antiphospholipid syndrome: expanding our understanding of antiphospholipid syndrome in children

Kevin Lewis[a], *Ajay Tambralli*[b,c] *and Jacqueline A. Madison*[b,c]

Purpose of review
Antiphospholipid syndrome (APS) is an autoimmune, thromboinflammatory disease, which affects children and adults. There are particular features of the disease and nuances to diagnosis and management in a pediatric population, which must be appreciated to improve clinical care.

Recent findings
Pediatric-specific epidemiological studies highlight that pediatric APS is quite rare with incidence in some populations of 0.2 per 100 000. There are new classification criteria in APS, which include a wider range of clinical features increasingly identified in registry data and case series of pediatric APS, though validation in pediatric APS is still needed. There is a particularly high proportion of pediatric APS patients with noncriteria antiphospholipid antibodies (aPL). Recurrent thrombosis is especially common in pediatric APS, highlighting the difficulty of management of this disease with high morbidity in children.

Summary
Recent research has enhanced understanding of pediatric-specific APS epidemiology, laboratory findings, the wide variety of clinical features, and challenges in successful treatment. Future directions could include evaluation of potentially unique features in pediatric pathophysiology, an evaluation of the new APS classification criteria in children, broader prospective data on clinical and laboratory features, and a continued search for treatment beyond committing young patients to lifelong anticoagulation.

Keywords
anticoagulation, antiphospholipid syndrome, pediatrics

INTRODUCTION

Antiphospholipid syndrome (APS) is a thromboinflammatory disease wherein patients develop thrombotic events, obstetric morbidity, and other complications in the presence of antiphospholipid antibodies (aPL). Though APS has been best studied in adults, the disease does occur in children and adolescents, potentially leading to complications for the rest of a young person's life. The pathophysiology, important features of which are highlighted in Table 1, has almost entirely been studied in adults with key features including the pathogenic role of antiphospholipid antibodies themselves and multiple abnormalities within the vasculature and the inflammatory response [1]. This review will identify updates in APS clinical care highlighting considerations specific to pediatric APS.

EPIDEMIOLOGY

The largest North American study of APS epidemiology in adults found an incidence of 2.1 per 100 000 and prevalence of 50 per 100 000 [12]. In a review of six studies from around the world, the incidence range was 1–2 per 100 000 and prevalence 40–50 per 100 000 [13]. The incidence is suspected to be lower in pediatrics; in one evaluation of 1000 patients with APS, only 2.8% were diagnosed at 15 years of age or younger [14]. In a unique study of pediatric APS, the authors estimated an incidence of 0.2 per 100 000 and a prevalence of 2.5 per 100 000 inhabitants in their region of Italy [15▪▪]. The authors of another recent study at a university hospital in Pakistan reviewed all thrombosis

[a]Division of Pediatric Hematology and Oncology, [b]Division of Pediatric Rheumatology, Department of Pediatrics and [c]Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to Jacqueline A. Madison, MD, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5352, USA. Tel: +1 734 764 2224; e-mail: madisonj@umich.edu

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KEY POINTS

- Pediatric antiphospholipid syndrome is a thromboinflammatory disease that affects multiple organ systems with high potential for morbidity and mortality.
- Recurrent thrombotic events are common, perhaps more so than in adults.
- Pediatric APS may benefit from its own classification criteria, because current adult classification criteria do not encompass all clinical features in pediatric APS.
- Laboratory testing for APS in pediatrics mimics testing in adults, but confirmation of persistent positivity is paramount.
- Treatment of pediatric APS is largely guided by anticoagulation recommendations derived from adult studies despite differences in pharmacokinetics, the need for weight-based dosing, and other considerations uniquely relevant to the pediatric population.

hospitalizations in children 0–18 years of age and identified that 9% were related to APS [16]. This percentage is consistent with adult data identifying that aPL may be positive in 10% of individuals with DVT, 11% with stroke, and 17% with stroke before age 50, though these studies could not always confirm persistent, strongly positive aPL [17].

In the largest pediatric APS series deriving from the European Ped-APS Registry, the mean age reported was 10.7 years (range 1–17) and there was a female-to-male ratio of 1.2 : 1 [18]. About half of the patients in this series and others [19] have 'secondary APS', a term applied to patients with another systemic autoimmune disease, most often systemic lupus erythematosus (SLE). This is in contrast to primary APS, in which no other concomitant diagnosis exists. In the Ped-APS Registry, 30% of patients diagnosed as having primary APS were later diagnosed with SLE or SLE-like disease at a mean 1.2 ± 1 years later [18]. This phenomenon of an APS diagnosis followed by the development of another autoimmune disease highlights how rheumatologists' broad evaluation for autoimmune disease adds to APS management.

DIAGNOSIS AND CLASSIFICATION

There are no diagnostic criteria for APS, but multiple rounds of classification criteria have been developed for research purposes. Until recently, the 2006 Sydney Classification Criteria were used to classify, and practically used to diagnose, patients with APS [20]. These criteria required the persistence of aPL (antiβ2 glycoprotein I IgG or IgM, anticardiolipin IgG or IgM, or a positive lupus anticoagulant functional assay, which screens for the presence of any aPL) over 12 weeks and the presence of a thrombotic event (arterial, venous, or small vessel) or specific types of obstetric morbidity. The 2023 ACR/EULAR APS classification criteria (Table 2) were recently developed to improve specificity [21▪▪]. The 2023 criteria consist of a weighted scoring system in both laboratory and clinical domains in order to classify as APS. The scoring system is more strict about thrombotic events occurring in the absence of other risk factors but more inclusive of several clinical features beyond thrombosis, such as thrombocytopenia and cardiac valve involvement. The lab criteria emphasize persistence of a lupus anticoagulant and the IgG isotypes of the anticardiolipin and antiβ_2GPI antibodies; having only IgM aPL, for example, would not provide enough points to fulfill the criteria. The aPL are expected to be measured by ELISA, with units more than 40 classified as positive. However, in routine clinical practice, these antibody

Table 1. Cells and systems implicated in the pathophysiology of antiphospholipid syndrome

Cells or system	Implications in APS
Neutrophils	Neutrophil extracellular trap (NET) formation (in which neutrophils eject webs of decondensed extracellular DNA and histones) is prothrombotic [2]. Calprotectin has been identified in pediatric APS as a biomarker of increased NETosis [3▪].
Endothelium	*In vitro*, aPL activate endothelial cells, increasing their expression of TF and cell adhesion molecules such as integrins and selectins [4–7].
Platelets	Platelet activation and crosstalk with leukocytes lead to increased inflammation and a prothrombotic state in APS. APS patients have more circulating platelet–leukocyte aggregates [1,8]. Antiβ_2GPI antibodies have been shown to activate platelets [9,10].
Complement	C5a leads to increased TF expression and membrane attack complex (C5b-9) formation, which together lead to increased platelet activation [11]. Disruption of the complement pathway leads to decreased thrombosis in APS animal models [1].

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; NET, neutrophil extracellular trap; TF, tissue factor.

Table 2. 2023 ACR/EULAR antiphospholipid syndrome classification criteria

Entry criteria: 1 clinical criterion and a positive aPL within 3 years of clinical criterion		
Classification criteria require three points from clinical domains and three points from laboratory domains		
Clinical criteria by domain		
Domain	Criteria	Weight
Microvascular	VTE with high-risk VTE profile	1
	VTE without a high-risk VTE profile	3
Macrovascular	Arterial thrombosis with a high-risk CVD profile	2
	Arterial thrombosis without a high-risk CVD profile	4
Microvascular	Suspected (one or more of the following): livedo racemosa (exam), livedoid vasculopathy lesions (exam), acute/chronic aPL-nephropathy (exam or labs), pulmonary hemorrhage (symptoms and imaging)	2
	Established (1 or more of the following): livedoid vasculopathy (pathology), acute/chronic aPL-nephropathy (pathology), pulmonary hemorrhage (BAL or pathology), myocardial disease (imaging or pathology), adrenal hemorrhage (imaging or pathology)	5
Obstetric	At least three consecutive prefetal (<10w) and/or early fetal (10/0–15/6) deaths	1
	Fetal death (33/6w) in the absence of PEC with severe features or PI with severe features	1
	PEC with severe features (<34w) or PI with severe features (<34w) with or without fetal death	3
	PEC with severe features (<34w) and PI with severe features (<34w) with or without fetal death	4
Cardiac Valve	Thickening	2
	Vegetation	4
Hematology	Thrombocytopenia (lowest 20–130 × 10^9/l)	2
Laboratory criteria by domain		
LAC	Positive LAC (single—one-time)	1
	Positive LAC (persistent)	5
aPL by ELISA (persistent)	Moderate or high positive IgM (aCL and/or aβ_2GPI)	1
	Moderate positive IgG (aCL and/or aβ_2GPI)	4
	High positive IgG (aCL or aβ_2GPI)	5
	High positive IgG (aCL and aβ_2GPI)	7

This table is a representation of the new criteria, and additional details can be found in the original publication [21▪▪]. In applying the criteria, only the highest criterion per domain may be counted. A clinical criterion may count if there is not an equally or more likely explanation than APS and there is a positive aPL within 3 years of the event. Notably, the definition of persistent lab findings is at least 12 weeks apart. A moderate titer aPL is 40–79 units on the solid phase assay (ELISA) and high titer is ≥80 units; these units are not the same on other testing modalities. aβ_2GPI, antiβ_2-glycoprotein-I; aCL, anticardiolipin; APS, antiphospholipid syndrome; BAL, bronchoalveolar lavage; CVD, cardiovascular disease; ELISA, enzyme-linked immunosorbent assays; LAC, lupus anticoagulant; PEC, preeclampsia; PI, placental insufficiency; VTE, venous thromboembolism.

tests may be done with multiplex assays or other techniques whose values do not always correlate with those from the ELISA-based tests.

The 2023 APS criteria improved upon the 2006 Sapporo classification in specificity, 99% compared with 86%, but lost sensitivity, 84% compared with 99% [21▪▪]. These new criteria have not yet been validated in pediatric APS, though there are efforts underway to assess their performance. Although the 2023 ACR/EULAR criteria cannot be formally used for diagnosis, they can help provide guidance in approaching cases of suspected pediatric APS. By including clinical criteria in addition to thrombosis, they may help clinicians sooner identify pediatric patients with APS.

LABORATORY MANIFESTATIONS

Lab testing for pediatric APS mirrors that of adult APS. Children may have higher rates of lupus anticoagulant positivity but similar rates of antiβ_2GPI and anticardiolipin positivity [18]. A recent systemic review demonstrated that the lupus anticoagulant was the most frequently detected aPL in children (75%) followed by anticardiolipin (IgG: 53%, IgM: 35%, either: 70%) and antiβ_2GPI (IgG 33%, IgM: 14%, either: 58%); the triple positive rate was 29% [15▪▪].

Risk stratification based on lab profile

In adults, the presence of a high-risk lab profile (lupus anticoagulant and/or antiβ_2GPI or anticardiolipin

antibodies ≥40 units) are most strongly associated with the development of thrombotic events [22]. In a study of 57 pediatric aPL-positive patients, a high-risk lab profile was identified in all 9 patients with a subsequent thrombotic event and most patients (93%) with noncriteria manifestations [23▪].

Noncriteria antibodies

Beyond antiβ_2GPI and anticardiolipin antibodies, there may be other aPL that bind to phospholipids or phospholipid-associated targets, such as phosphatidylethanolamine, phosphatidylserine, and prothrombin [24–27]. Antiphosphatidylserine/prothrombin (anti-PS/PT) antibodies that recognize complexes of phosphatidylserine and prothrombin can cause a positive lupus anticoagulant and be tested in commercial labs [28–30]. Sloan *et al.* [3▪] found that pediatric APS patients had high rates of anti-PS/PT IgG/IgM (58 and 68%, respectively) and a strong association with thrombotic events, thrombocytopenia, and hemolytic anemia, consistent with adult studies [31–33]. Antibodies against domain I of β_2GPI were also common and correlated with thrombocytopenia, hemolytic anemia, and livedo reticularis/racemosa [3▪]. Anti-PS/PT IgG/IgM and antiβ_2GPI domain I IgG may be especially valuable when lupus anticoagulant testing is unreliable due to some forms of anticoagulation.

Testing for antiphospholipid antibodies persistence

Children may have transiently positive aPL for a variety of reasons, either incidentally or in the context of upper respiratory infections, vaccinations, or exposure to nutritional antigens [34]. In the Kids-DOTT trial of patients younger than 21 years of age with an acute *provoked* VTE and a positive aPL, the authors found that 22% of all patients had positive aPL at enrollment, but after 6 weeks, only 10% of those with an initial positive aPL had a persistently positive aPL, though 30% had no repeat testing [35▪▪]. Patients with persistent aPL were older (16 vs. 10 years median age) and had a higher risk of recurrent VTE (18 vs. 1%, OR 12.2). This study reinforces the recommendation to repeat testing to ensure durability of aPL.

CLINICAL MANIFESTATIONS

The most common clinical manifestation reported in pediatric APS is thrombosis. In a meta-analysis of five pediatric APS studies with 30 or more participants, the pooled point prevalence rate of thrombosis, arterial thrombosis, venous thrombosis, and stroke was 98.2, 27.6, 51.1, and 13.4% [36▪]. A recent systematic review and pooled meta-analysis of nine studies of pediatric APS including 352 patients reported recurrence of thrombosis in 27% of patients over a median follow-up of 2.6–5.8 years [37▪▪]. There was no significant difference between primary and secondary APS patients, nor depending on whether the index thrombotic event was venous or arterial. The authors also found an incidence proportion of mortality at 0.07 with 8 of 10 deaths due to recurrent thrombotic events. Another report of 30 patients with pediatric APS identified a recurrent thrombotic event in 32% of patients, a third of whom were on therapeutic anticoagulation, and the 1-year and 5-year recurrent thrombosis-free survival in the cohort was 78 and 68%, noted to be lower than in reports of adults [38]. Recurrent thrombosis is a particularly important issue in pediatric APS.

Registry data and many case series have identified many other clinical characteristics seen in pediatric APS, often referred to as 'noncriteria' manifestations, which were not included in the Sydney criteria, though some are now included in the 2023 ACR/EULAR criteria (Fig. 1 and Table 2). Hematologic manifestations including thrombocytopenia, autoimmune hemolytic anemia (AIHA), Evans syndrome (both thrombocytopenia and AIHA), and lupus anticoagulant hypoprothrombinemia syndrome are frequently reported, for example, at 38% in the large Ped-APS registry [18] and 42% in a cohort of aPL-positive children [39]. Also particularly common are a wide variety of neurologic features, skin changes, and kidney disease [18].

Catastrophic antiphospholipid syndrome

Catastrophic APS (CAPS) is a particularly dangerous presentation of APS in which rapid, widespread small vessel thrombosis leads to multisystem dysfunction and potentially organ failure or death. From registry data of 45 children compared to 401 adults, pediatric CAPS occurred more often as the first manifestation of APS (87 vs. 45.2%) and after an infectious trigger (60.9 vs. 26.8%), but there were few other differences, and mortality was high at 26% [40].

Neonatal antiphospholipid syndrome

APS is exceptionally rare in the neonatal population, whether in association with or independent of maternal aPL [41,42]. In a review of 134 neonates born to mothers with APS, there were no cases of neonatal thrombosis or lupus, all aPL matched the maternal profile, and most aPL cleared within

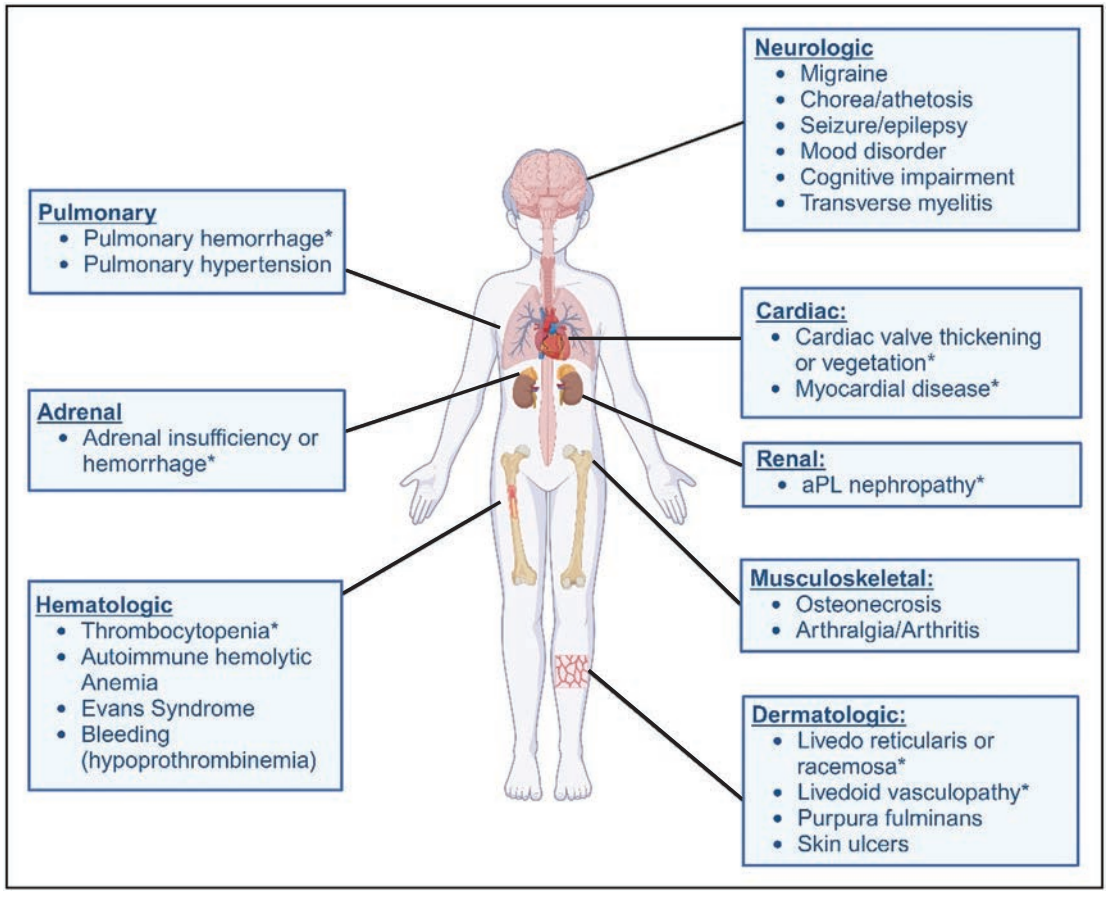

FIGURE 1. The spectrum of clinical characteristics of pediatric antiphospholipid syndrome. Pediatric patients with APS experience a wide variety of clinical presentations beyond thrombosis. Displayed are many of the common or significant clinical features described in case series of pediatric APS. Clinical features with ∗ indicate those included in the 2023 ACR/EULAR classification criteria. aPL, antiphospholipid antibody; APS, antiphospholipid syndrome.

6 months [43], but several studies have reported neurodevelopmental disorders in children born to mothers with APS [44,45].

MANAGEMENT

There are no FDA-approved treatments specifically for pediatric APS, so all therapies discussed below are off-label.

Primary prevention

Patients may have aPL identified before any thrombotic or other major clinical event, for example, in working up a prolonged PTT or in lupus patients. Primary thromboprophylaxis focuses on modifiable thrombotic risk factors: obesity, hypertension, tobacco use, precautions around prolonged immobilization, and avoiding systemic estrogen therapy as in combined OCPs [46]. Contraception can be safely achieved through methods such as nonestrogen-containing contraceptives like progestin-only OCPs and intrauterine devices [46].

Low-dose aspirin (LDA), which irreversibly inhibits platelet function, has been considered for use in thrombotic prophylaxis in aPL-positive individuals without definite consensus. For those pediatric patients with SLE and aPL, the SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) initiative, a European consensus panel of experts, recommended consideration of adding LDA to their regimen in addition to hydroxychloroquine [47]. In APS, a meta-analysis demonstrated a significant decrease in the risk of a first arterial thrombotic event in those taking LDA, especially in obstetric APS and concomitant SLE [48], but the only randomized controlled trial, limited by low-event rate, demonstrated no benefit [49]. We take an individualized approach educating patient families on this nuance, but unless there are increased bleeding risks, we often add LDA in the case of a patient with persistent strong positive aPL, especially lupus anticoagulant or IgG aPL.

Secondary prevention

LDA is not sufficient treatment for secondary prevention; multiple studies have demonstrated a lower risk for recurrent thrombosis with vitamin K antagonists (VKA) such as warfarin compared with LDA [50,51]. After an initial thrombotic event, pediatric patients are typically started on either low-molecular-weight heparin (LMWH) or unfractionated heparin often followed by a transition to warfarin, though for some children remaining on a heparinoid is preferable (Table 3) [47,52▪▪]. The INR goal in APS is typically 2–3; two randomized control studies did not show increased effectiveness with a higher INR goal of 3–4 and instead demonstrated more bleeding [58,59]. Chromogenic factor X (CFX) testing, can confirm INR readings are accurate without interference from a lupus anticoagulant effect [53,60]. In our practice, we check CFX early in diagnosis than intermittently for patients on VKA.

There has been interest in the use of direct oral anticoagulants (DOAC), but large, randomized controlled trials in adult APS patients treated with DOACs vs. warfarin showed a higher rate of thrombotic events in the DOAC arm [55–57]. Adding aspirin to warfarin therapy for patients with arterial thrombosis is sometimes employed, but a randomized controlled trial of adults treated with aspirin showed increased bleeding events without reduced thrombotic events [61–63], so this strategy must be used with caution.

Other therapies

Management in APS largely focuses on treating the thrombotic risk, but there are some therapies, mostly adjunctive, that address the underlying inflammatory pathways. Hydroxychloroquine has been associated with lowering aPL levels in primary and secondary APS [64,65], and in one small nonrandomized trial of APS patients, the addition of hydroxychloroquine to anticoagulation led to lower thrombotic events [66]. Statins are widely used for other cardiovascular indications, and one retrospective cohort study suggested a protective effect against thrombosis in aPL-positive individuals [67]. A small trial of coenzyme Q10 (ubiquinol) improved mechanistic endpoints [68]. To target complement pathways, case reports of eculizumab, a C5 inhibitor, suggest some, but not universal, success in refractory pediatric CAPS [69–71].

Because of the pathogenic effects of aPL themselves, several therapies that address B-cell production of aPL have been assessed. In adults, an open-label phase II trial of 20 patients given rituximab suggested benefit in treating small vessels, such as skin ulcers and aPL nephropathy [72]. Evidence for

Table 3. Anticoagulants used in the treatment of antiphospholipid syndrome

Anticoagulant	Mechanism of action	Therapeutic considerations	Side effects/drawbacks
Warfarin (coumadin)	Vitamin K epoxide reductase inhibitor (vitamin K antagonist)	First-line thromboprophylaxis after initial thrombotic event (requires bridging with heparin or LMWH).	Risks include increased bleeding, frequent INR monitoring (initially three times weekly), INR variations from diet, difficulty with weight-based dosing with pill formulation, and drug–drug interactions [52▪▪].
Low-molecular-weight heparin (enoxaparin)	Inactivates factor Xa (through complex formation with Antithrombin III)	First line in neonatal APS due to ease of weight-based dosing. Common initial therapy in pediatrics prior to warfarin initiation.	Risks include increased bleeding, typically twice per day dosing, subcutaneous administration, and weekly lab draws and monitoring [46,47].
Unfractionated heparin	Inactivates factor Xa (through complex formation with Antithrombin III)	Optional use in the initial stage of anticoagulation similar to LMWH.	Drawbacks include increased bleeding risk and typically being given intravenously and thus not feasible for outpatient use. Subcutaneous heparin is available, but LMWH is the preferred SC formulation [46,47].
Aspirin	Inhibits cyclooxygenase (blocks thromboxane A2 production, leading to irreversible platelet function inhibition)	Typically adjuvant therapy with warfarin with recurrence and/or arterial thrombosis [53].	Risks include increased bleeding, increased risk of Reye's syndrome and being insufficient for full anticoagulation [54].
DOAC (rivaroxaban, dabigatran, apixaban)	Inhibits factor Xa (Rivaroxaban and Apixaban) or thrombin (Dabigatran)	Not recommended for APS.	Studies in adults have shown increased rates of recurrent and breakthrough thrombosis with DOAC monotherapy compared to warfarin [55–57]

APS, antiphospholipid syndrome; DOAC, direct oral anticoagulant; INR, international normalized ratio.

the use of rituximab in children has been limited to case reports demonstrating success in treating certain manifestations including CAPS [73], chorea [74], and lupus anticoagulant hypoprothrombinemia syndrome [75]. Daratumumab, a monoclonal antibody targeting CD38 approved for use in multiple myeloma, has the potential to more completely lead to aPL depletion; one case report of a 21-year-old with APS described safety and significantly decreased aPL over 3 months [76]. A larger study of daratumumab in APS (NCT05671757) is underway. This phase 1b study seeks to determine safety of use while also determining whether aPL are eliminated. Another emerging category of treatment is cellular therapy. In APS, evidence is limited thus far to one case report: a 65-year-old woman with SLE and triple positive APS who developed lymphoma treated with anti-CD19 CAR-T cells led to lymphoma remission and normalization of all aPL [77▪].

Recurrent thrombosis

If recurrent thrombotic events occur despite therapeutic anticoagulation, then consideration is given to changing anticoagulation strategy, adjusting the INR goal, adding aspirin for arterial thrombosis, or adding adjunctive therapies [53]. We recommend first ensuring therapeutic anticoagulation and troubleshooting with the patient, family, and hematology. If there is an arterial thrombotic event, we may add aspirin. We often add hydroxychloroquine if not already employed and consider other adjunctive strategies.

Catastrophic antiphospholipid syndrome treatment

Treatment of CAPS consists of what is termed 'triple therapy' with anticoagulation, intravenous glucocorticoids, either plasmapheresis or IVIG, and management of any inciting event [47,78]. Rituximab is another consideration for pediatric CAPS due to success in case reports and a nonstatistically significant higher rate of survival in the children in the CAPS registry [73,79]. Our approach is individualized, but we frequently add rituximab to triple therapy for CAPS.

Nonpharmacologic measures

All patients should be educated on cardiovascular health and provided with recommendations to control modifiable risk factors. A scoping review on rehabilitation interventions for APS identified possible success of exercise in pediatric APS and lupus [80] and opportunity for a multidisciplinary approach to symptoms unresolved by anticoagulation [81].

CONCLUSION

Pediatric APS remains an understudied field. There are particular considerations in this age group related to the applicability of adult classification criteria to children, the rates of transient autoantibody positivity in children, high rates of recurrent thrombosis, and limitations of available treatment choices. Patients and clinicians would benefit from future research targeting the underlying pathophysiology specific to pediatric APS, applicability of classification criteria in children, and a broader array of effective treatments.

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Conflicts of interest

There are no conflicts of interest.

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Isolated aortitis – is it truly isolated? An approach to diagnosis and management

Ora Gewurz-Singer[a] *and Elizabeth Lee*[b]

Purpose of review
With the rise in incidence of aortic aneurysm surgeries and the advances in large vessel imaging's ability to detect vessel wall inflammation, rheumatologists can expect to see an increase in isolated aortitis (IA) cases in their clinics. The purpose of this article is to review the latest data on IA, discuss its natural history and to provide an approach on how to diagnose and manage this inflammatory aortic disease.

Recent findings
IA can be diagnosed on surgical histology or on imaging studies. Preoperative imaging in patients with thoracic aortic aneurysms does not detect all aortitis cases. Patients with IA have a high risk (up to 50%) of developing new aortic and branch lesions. Histologic and mechanistic studies show an overlap with giant cell arteritis.

Summary
Evaluation for underlying infections and systemic diseases is recommended for diagnosis. Surveillance of patients with IA with repeated clinical assessments and imaging is recommended.

Keywords
clinically isolated aortitis, isolated aortitis, large vessel vasculitis

INTRODUCTION

Aortitis is inflammation of the wall of the aorta. Isolated aortitis (IA) is a form of aortitis that is not associated with an underlying systemic vasculitis or other inflammatory condition. With the significant rise in surgical procedures for thoracic aortic aneurysms [1,2] and advances in imaging that can detect aortic inflammation, rheumatologists can expect to see more IA cases in their practices. This article will review our understanding of IA and its natural history and will present an approach to the diagnosis and management of patients with this disease.

DEFINITION AND NOMENCLATURE

There is no consensus definition of IA. No diagnostic criteria to use in clinical practice nor classification criteria to distinguish IA from other forms of aortitis are available. This condition has been referred to in the literature using various terms including focal isolated aortitis, idiopathic aortitis and nonsyndromic aortitis. According to the *2012 Chapel Hill Nomenclature System for Vasculitis* IA is a single organ vasculitis [3] which by definition '*has no features that indicate that it is a limited expression of a systemic vasculitis*.' One might expect that by definition IA would be anatomically isolated to the aorta, however this precept is not uniformly accepted, and many IA cohorts include patients with branch vessel involvement [4▪,5]. The term *clinically isolated aortitis* (CIA) was suggested in a 2015 international consensus statement on aortitis and refers to IA identified on surgical pathology [6]. The diagnosis of IA can be made histologically after surgical resection or by the presence of aortic wall inflammation on magnetic resonance (MR), computed tomography (CT) or ^{18}F-fluorodeoxyglucose positron emission tomography (PET) imaging. This article adheres to the convention accepted by some experts of using the term CIA for histologically detected cases and IA for cases identified on imaging.

[a]University of Michigan, Department of Medicine, Division of Rheumatology and [b]University of Michigan, Department of Radiology, Ann Arbor, Michigan, USA

Correspondence to Ora Gewurz-Singer, MD, MS, 300 N Ingalls Building, 7C27 Suite, Ann Arbor, MI 48109-5422, USA. Tel: +1 734 936 5566; e-mail: singero@med.umich.edu

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KEY POINTS

- Isolated aortitis is a diagnosis of exclusion and work up should be pursued for an underlying systemic disease.
- Up to 50% of patients with clinically isolated aortitis diagnosed on a resected aneurysm will go on to have another arterial event.
- Some isolated aortitis cases might represent a variant of giant cell arteritis.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Much of our knowledge about IA comes from surgical series of thoracic aortic aneurysm resections published over the past two decades [4▪,5,7–10,11▪▪,12–22]. Noninfectious aortitis is found in 2 to 7% of thoracic aortic aneurysm specimens. CIA accounts for approximately two-thirds of these cases [21–23]. In a large series from Cleveland Clinic of 7511 thoracic aortic surgical specimens, 196 (2.5%) histologically proven aortitis cases were identified. The majority of these (66%) were CIA [23]. Results from a French group were similar with 217 aortitis patients found amongst 5666 (3.8%) thoracic aortic surgical cases and 118 (54%) were identified as CIA [11▪▪].

The percentage of IA amongst all aortitis cases is likely overestimated in surgical series. Interestingly, IA is less common in cohorts of aortitis diagnosed on imaging, accounting for only approximately a quarter of aortitis cases [24,25]. In a French series, 44 cases of IA were identified amongst a total of 154 cases of noninfectious aortitis (28%) diagnosed on imaging [11▪▪].

CIA presents more commonly in women (53 to 73%), in their sixth to seventh decade of life (median age 62–74 years old) [5,7,9,15,17,18]. In a case-controlled study of 42 CIA patients diagnosed on histology and 219 matched controls, multivariable analysis showed that older age, female gender, absence of known coronary artery disease, and larger sized aneurysms were risk factors for aortitis on biopsy [17]. More studies are needed to establish if these characteristics might serve as a clue for surgeons to the need for preoperative rheumatology referral.

The majority of patients with histologic diagnoses of CIA are asymptomatic at presentation [17,18] while up to 40% of imaging-diagnosed IA patients are symptomatic. In one radiographic series 34.1% of patients presented with weight loss and fever [25].

Due to their retrospective design, most of the surgical series did not have access to preoperative Westergren's estimated sedimentation rate (ESR) and C-reactive protein (CRP) values. Those studies that did, found patients with histological CIA had normal inflammatory markers [4▪,9,11▪▪,24]. In imaging diagnosed IA, elevated ESR and CRP are typically used as part of the diagnostic criteria for aortitis thus not surprisingly in these series ESR and CRP were found to be elevated [15,20].

This discordance in incidence of IA in surgical vs imaging-based cohorts as well as the differences in their presentation has raised the question whether histologically and imaging diagnosed IA represent a spectrum of the same disease or are two separate entities [26]?

DIAGNOSIS

IA is a diagnosis of exclusion. Whether it is detected on postoperative pathology in an asymptomatic patient or suspected on imaging studies in a patient with elevated inflammatory markers, additional work up examining for involvement of other vascular beds as well as to rule out infection and systemic forms of vasculitis should be performed.

Differential diagnosis

Aortitis is defined by transmural (involving all three layers) inflammation of the aortic wall. It is distinguished from periaortitis which is limited to the adventitia, the outermost layer [6]. The differential diagnosis for aortitis is broad (Table 1). It is important to recognize that atherosclerosis can also cause inflammation of the aortic wall and might mimic aortitis both on histology and imaging studies. Consideration of atherosclerotic aortic disease should be given to those with known coronary artery disease or risk factors for atherosclerosis as well as those with high vascular calcium burden seen on imaging.

Infectious causes of aortitis should be considered. The most common bacterial infections of the aorta are staphylococcus, streptococcus, salmonella, pseudomonas, syphilis and coxiella brunetti (Q-fever). Fungal, viral and mycobacterial pathogens are less common.

Systemic rheumatic diseases that can present with aortitis (Fig. 1) are divided into primary and secondary vasculitites. Giant cell arteritis (GCA), Takayasu arteritis (TA), Behcet's disease (BD), relapsing polychondritis and Cogan's syndrome (CS) are all primary large vessel vasculitites. Rarely antineutrophil cytoplasmic antibody associated vasculitis, which is a small vessel vasculitis, can involve the aorta and its branches. Diseases that can cause a secondary aortitis include systemic lupus erythematosus, ankylosing spondylitis and rheumatoid

Table 1. Differential diagnosis for aortitis

	Associated signs and symptoms	Histologic pattern
Atherosclerosis	History of CAD or PAD, calcification on vascular imaging	
Infection (*Staphylococcus, streptococcus*, salmonella, pseudomonas, syphillis, coxiella brunetti, mycobacteria or fungi)	Pulsatile mass, fever, chills, night sweats, sepsis	Supportive
Primary vasculitites		
Giant cell arteritis	Age >50, headache, jaw pain, visual disturbance, scalp tenderness, PMR symptoms	Granulomatous
Takaysu arteritis	Age < 50, claudication, constitutional symptoms	Granulomatous
Behcet's disease	Oral and genital ulcers, inflammatory eye disease, rashes, pathergy, inflammatory bowel disease	Mixed inflammatory
Cogan's syndrome	Inflammatory eye disease, autoimmune hearing loss	Mixed inflammatory
Relapsing polychondritis	Ear and/or sinus chondritis, laryngeal stenosis, arthralgia	Mixed inflammatory
ANCA vasculitis	Sinonasal disease, inflammatory eye disease, rashes, pauci immune glomerulonephritis, interstitial lung disease, granulomas, neuropathy	Granulomatous
Secondary vasculitites		
Systemic lupus erythematosus	Malar or other rash, oral sores, alopecia, serositis, arthritis	Lymphoplasmacytic
Rheumatoid arthritis	Arthritis, rheumatoid nodules	Granulomatous
Ankylosing spondylitis	Inflammatory back pain and/ or inflammatory eye disease	Lymphoplasmacytic
Periaortitis		
IgG4 sclerosing disease	Lymphadenopathy, swollen glands, pancreatitis	Lymphoplasmacytic
Sarcoidosis	Lymphadenopathy, E. nodosum, rashes	Granulomatous
Retroperitoneal fibrosis	Back pain, urinary obstruction	
Histiocytosis	Variable presentation	
Radiotherapy	History of radiation to the chest	

CAD, coronary artery disease; PAD, peripheral artery disease; PMR, polymyalgia rheumatica.

arthritis. Sarcoidosis, immunoglobulin G4 (IgG4) sclerosing disease and retroperitoneal fibrosis can present with periaortitis.

The segment of the aorta involved as well as the predilection for particular aortic branch arteries can serve as clues to an underlying systemic disease. IA typically involves the thoracic aorta, and particularly the root, ascending and arch segments. In surgical series, up to 95% of cases involve the ascending aorta [11▪▪,17]. Though describing the angiographic patterns of each of the vasculitites is beyond the scope of this article, it is important to look at the entire aorta and its branches and use the anatomic distribution to guide the diagnosis.

Histology

When histology is available, it might be helpful in differentiating between the various causes of aortitis. There are 4 histologic subtypes of inflammatory aortitis [6]. The suppurative pattern is associated with infectious aortitis has neutrophil infiltration and necrosis. The granulomatous pattern, also called the giant cell subtype, has clusters of epithelioid macrophages with or without giant cells and well formed granulomas. The lymphoplasmocytic pattern has lymphocyte and plasma cell infiltration without granulomas and giant cells. The mixed inflammatory pattern has a mix of cell types. Each histologic subtype associates with different aortitis diagnoses (Table 1).

Though patients with IA can have any of the 3 noninfectious aortitis histologic subtypes, the granulomatous or giant cell pattern is most common. Of surgical pathology cases, 62 to 84% have granulomatous inflammation and/or giant cells [4▪,5,8,9, 11▪▪,14].

Recommended work-up

Details about the work up of aortitis are outlined in (Table 2). A thorough history and physical exam is recommended to evaluate for signs and symptoms of the diseases on the differential diagnosis.

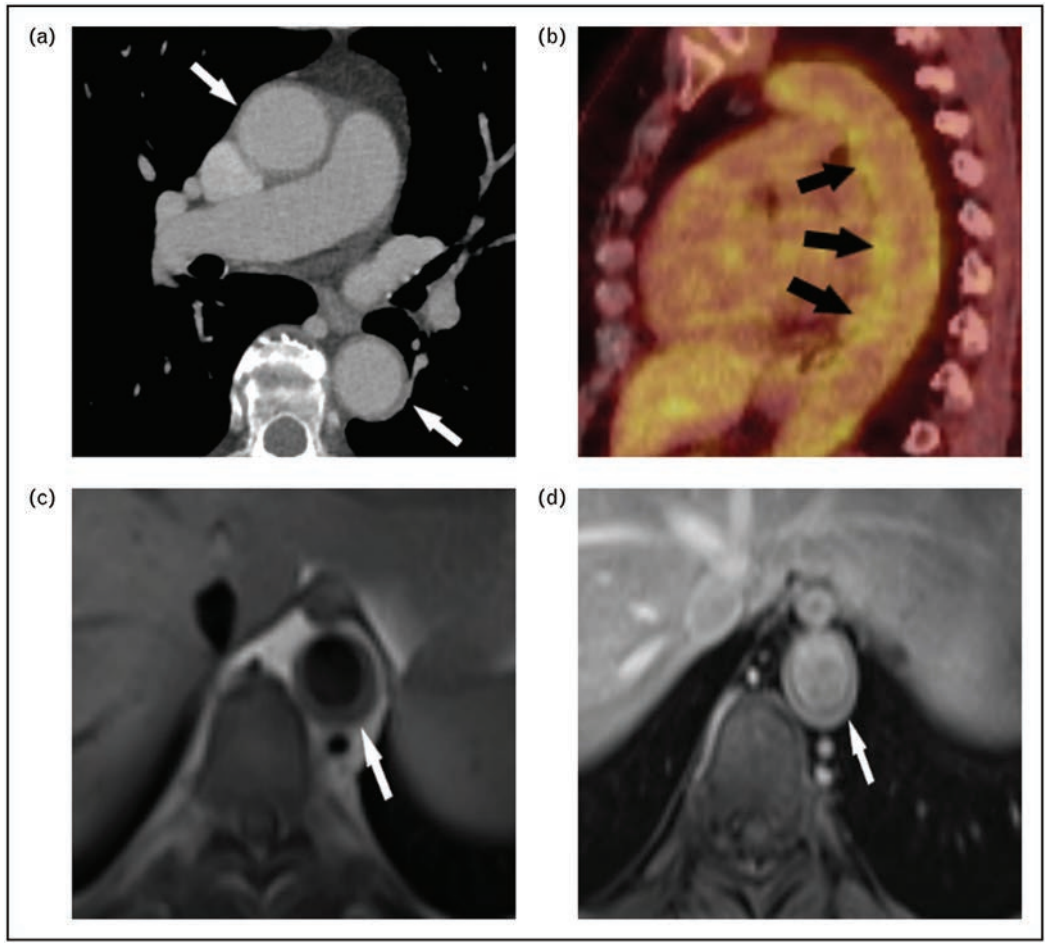

FIGURE 1. Imaging findings of aortitis. (a) Axial contrast enhanced CT image with mild circumferential wall thickening and enhancement in the involving both the ascending and descending thoracic aorta (arrows), (b) FDG uptake on PET (arrows) descending aorta on sagittal fusion PET-CT images. (c) MR findings of aortitis include wall thickening on axial black blood T1-weighted; (arrow) and wall enhancement (d) on axial T1-weighted fat saturation post contrast, arrow).

Laboratory evaluation should be directed based on the findings from the history and physical exam (Table 2). Imaging should include arteries of the neck, chest, abdomen and pelvis. In older patients (>50 years old), GCA is high on the differential diagnosis. In addition to questions about cranial symptoms (headaches, visual disturbance, jaw claudication, scalp tenderness) and polymyalgia rheumatica, it is also reasonable to pursue imaging with temporal artery ultrasound or MR of the cranial arteries or to consider a temporal artery biopsy.

IS CLINICALLY ISOLATED AORTITIS JUST A VARIANT OF GIANT CELL AORTITIS?

Of interest, the histology of granulomatous CIA is indistinguishable from that seen in GCA in both temporal arteries and giant cell aortitis. The authors, Talarico *et al*. in their 2014 article have asked '*IA and GCA; are they really two sides of the same coin*' [20]? Their study, though small, suggests that when compared to a GCA control group, 11 imaging diagnosed IA patients were younger and more commonly male [20]. These findings are not in line with most series which show CIA more commonly in older women. In a French study comparing 73 patients with GCA to 44 with IA, the subgroup of IA patients >60 years-old had similar mean age, female predominance, inflammatory marker levels and risks for aortic complications as the GCA patients [25].

Older autopsy studies, also suggest that CIA might be a variant of GCA. In an autopsy series from Northern Europe, of 13 cases of noninfectious aortitis, 10 (77%) lacked clinical symptoms of vasculitis prior to death and thus might reasonably be given a diagnosis of CIA. However, 9 of the 10 also had inflammation found in the temporal arteries consistent with asymptomatic or subclinical GCA [27].

Mechanistic studies have also shown overlap between the pathogenesis of CIA and GCA. In the

Table 2. Work up of aortitis to consider

Laboratory studies
CBC, aerobic, anaerobic and fungal blood cultures, procalcitonin, RPR, Quantiferon Gold, Coxiella Brunetti IgG
ESR & CRP
ANA, ENA, C3, C4, dsDNA, RF, CCP, ANCA
Serum IgG4
HLAB-27
Imaging Studies
Of the entire aorta and its branches with CTA, MRA or PET
Temporal artery ultrasound
Sacroiliac joint imaging, X-rays of the hands and feet
Tissue studies
Temporal artery biopsy
Other biopsy pending imaging findings (i.e. lymphadenopathy, retroperitoneal inflammation)
Consider special staining for fungi/mycobacteria, IgG4 plasma cells, CD68, S100, CD1a and CD207

ANCA, antineutrophilic antibodies; CBC, complete blood count; CCP, cyclic citrullinated peptides; dsDNA, double stranded; RF, rheumatoid factor; RPR, rapid plasma regain; ANA antinuclear antibody, extractable nuclear antigens.

first global transcriptomics study comparing inflammatory and non-inflammatory aortic aneurysms, which included 8 GCA/PMR patients and 17 CIA patients, there was no difference in gene expression profiles between GCA/PMR and CIA [28]. A recent pilot study measured circulating Neutrophil Extracellular Trap (NET) markers and endothelial activation markers in plasma from patients with CIA [17], TAK ($n=7$), and GCA ($n=11$). Calprotectin, a known marker of NETosis and VCAM-1 were elevated in both CIA and GCA. Of note ICAM-1 was only elevated in CIA. Given the advances in treatment for GCA, knowing that a portion of IA patients might represent an alternative presentation of GCA, will change how we manage these cases [29▪]. More mechanistic studies are needed.

IMAGING STUDIES

Advances in imaging techniques have allowed for use of noninvasive testing to diagnose aortitis and monitor activity. Despite this progress, many unanswered questions remain. Which modality, CT, MR or FDG-PET is best for diagnosis and/or for monitoring disease? No standardized imaging protocols exist resulting in a range of image practices between centers. Furthermore, there is no consensus on interpretation of these studies or on an imaging definition of aortitis. How to distinguish active mural inflammation from scarring remains elusive.

Radiology series in IA [15,20,24,25,30▪▪] have used vessel wall thickness (>2 or 3 mm) and enhancement on CT or MR as well as increased FDG uptake (not explained by atherosclerosis) on PET as surrogate markers of aortitis. This is in line with current practices in diagnosing large vessel GCA and TAK arteritis (Fig. 1).

Gleaning imaging data from surgical cohorts is limited by their retrospective designs and the lack of uniformly available imaging for analysis. Of interest, imaging might not be sensitive enough to detect all aortitis. In two separate series of histologically diagnosed CIA, preoperative imaging did not show signs of aortitis. Comparing 23 histologically diagnosed CIA and 48 GCA patients, none of the CIA patients versus 57% of the GCA patients had >3 mm thickness of aortic wall on preoperative MR. Of those who had preoperative PET scans, 0/4 CIA patients had FDG uptake compared to 9/13 (69%) GCA patients [24]. In a more recent small study of 16 patients with various types of histologically proven noninfectious aortitis (4 with CIA), 31% did not have FDG uptake preoperatively on PET scan. Results for the 4 CIA patients were not reported. These findings might suggest that screening the 'high risk' patients (older women, without CAD and with fast growing larger aneurysms) preoperatively with PET might not be fruitful [30▪▪].

PROGNOSIS

Short-term postoperative outcomes from aortitis and nonaortitis aortic aneurysm resections are comparable. A study from Australia which compared resection of non-inflammatory aneurysms to those with noninfectious aortitis (66% were CIA) showed no difference in 30-day mortality, significant morbidity or infection rates [8]. Furthermore, withholding corticosteroids in this postoperative period from the aortitis patients did not lead to more adverse outcomes. Supporting these findings, in another study of 53 CIA patients compared to 109 matched controls there was no difference in postoperative complications, or need for surgical revision [5].

Longer term prognosis is difficult to assess from series as follow up periods differ, there is variability on outcome measures of aortic events and on availability and frequency of surveillance imaging.

Focusing on surgical series, the key question is once patients have their inflamed aneurysm resected, what is their risk of developing new lesions? Several studies have shown that the rate of subsequent vascular event is higher in aortitis than in the nonaortitis population [5,22]. Using pooled results from 4 surgical cohorts Stone et. al. estimates an event rate of approximately 8% per year for CIA patients compared to 0.7% for nonaortitis

patients [26]. In a recent study from Cleveland Clinic of 118 CIA patients, 16.1% developed new aneurysms and an additional 8.5% new vascular lesions in a mean follow-up of 3.9 years [31]. In that time, 16% of these patients were reclassified as having a systemic disease. These numbers are consistent with those from earlier cohorts where new or worse vascular events occur in 12 to 50% of CIA patient in a mean duration of 3.75–4.8 years [9,12,13,22].

The benefit of postoperative corticosteroid (CS) use remains an area of controversy. There seems to be a trend in reduced rates of new lesions in those treated. In a study of 196 patients with aortitis, 129 with CIA, 11 were treated with CS and only 2 (18%) had new lesions compared to 27 of 54 (50%) untreated CIA patients. However, two recent studies showed no association between postoperative initiation of glucocorticoids and future vascular outcomes [1,5,31]. More research is needed in this area.

Findings from imaging series suggest that IA has a higher rate of new vascular lesions to GCA [7,24,25]. The concern with this conclusion is that these studies include GCA patients with isolated cranial disease who do not have aortic involvement at baseline so risk of new lesion might be expected to be lower. Like in histologic series, in the imaging series there is also a trend towards reduced rates of subsequent lesions with corticosteroid treatment, but numbers are small and no conclusions can be drawn. Little can be concluded about the benefit of using steroid sparing agent in IA. Studies on disease modifying antirheumatic drugs and biologic agent use typically include all types of noninfectious aortitis and thus are not extrapolatable to IA [7].

RECOMMENDATIONS FOR MANAGEMENT

Suggestions for management relies on expert opinion, using the limited data we have to support decision making. Whether the diagnosis is made histologically or on imaging, it is critical to confirm the diagnosis by ruling out other causes of aortitis which might have a known treatment paradigm. Baseline imaging of the entire aorta and its' branches should be performed. Cardiovascular risk factors should be managed including treatment of obesity, hypertension, hyperlipidemia and tobacco abuse. Statin use has been shown in one study to reduce risks of subsequent arterial events [11▪▪]. As mentioned, the benefit of CS or other immunosuppression is unknown. It would be reasonable to consider CS use in IA patients with an inflammatory phenotype, those with symptoms, elevated inflammatory markers or multiple baseline lesions. More studies are needed in this area. The overlap in pathology between GCA and granulomatous IA as well as mechanistic studies suggesting similarities to GCA, make it reasonable to consider using agents effective in GCA in patients with granulomatous pattern CIA and perhaps in older patients with an inflammatory presentation. Surveillance for new vascular lesions and conversion to a systemic disease is critical. This includes history and physical for new signs and symptoms, routine laboratory testing and repeat large vessel imaging. How often to image is unclear at this time, consideration can be given to every 6 months for a year and if stable annually.

CONCLUSION

Patients with IA, even those whose lesions have been resected, can develop new vascular lesions. Though clinical risk factors might help identify aortitis preoperatively, studies have shown that imaging is not fully sensitive to identify aortic wall inflammation. More cases are being identified on advanced imaging. Histologically and imaging diagnosed patients might represent different diseases. Furthermore, a subgroup of IA patients might have an alternative presentation of GCA. Mechanistic studies are needed to help subtype patients to identify who will progress and who might benefit from immunosuppressive treatment.

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Conflicts of interest

There are no conflicts of interest.

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An update on the pathogenesis of idiopathic inflammatory myopathies

Eleni Tiniakou

Purpose of review
As the question of the pathogenesis of inflammatory myopathies remains unanswered, there has been a significant effort in recent years to investigate various components of the innate and adaptive immune systems, with evidence pointing that they work together to initiate and propagate the autoimmune response. This review aims to explore recent advancements in understanding the mechanisms underlying myopathies.

Recent findings
Recent research has concentrated on uncovering potential triggers, examining the role of immune cells, both lymphocytes and myeloids, and investigating the contribution of inflammatory mediators to the autoimmune response in inflammatory myopathies. Unsuccessful clinical trials helped reshape established hypotheses about pathogenesis, while genetic mutations offered clues to the disease's root causes. The pathogenic role of autoantibodies is being reconsidered based on transcriptional data. Repurposing existing medications to combat muscle fiber dysfunction is also emerging as a potential therapeutic approach.

Summary
Our understanding of inflammatory myopathies has evolved significantly as our understanding of the disease has grown. Even though breakthroughs have been documented on the underlying mechanisms of myopathies, important questions remain unanswered.

Keywords
antisynthetase syndrome, dermatomyositis, idiopathic inflammatory myopathies, immune mediated necrotizing myopathy, juvenile dermatomyositis, pathogenesis

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) represent a heterogeneous group of autoimmune syndromes characterized by skeletal muscle inflammation and proximal muscle weakness, with or without skin involvement. This definition, initially proposed by Bohan and Peter in 1975 [1,2], has evolved significantly as our understanding of the disease has grown. We now know that muscle inflammation can present in various patterns, often as part of a multisystemic disease, and can be defined by the presence of myositis-specific autoantibodies (MSAs), which help identify more homogenous groups with a similar phenotype [3]. These distinctions are important as diverse pathogenetic mechanisms are probably in place and different groups can respond to different medications, thus allowing for a more targeted treatment approach. Therefore, the differentiation of IIM into subtypes, either as dermatomyositis (DM), immune-mediated necrotizing myopathies (IMNM), antisynthetase syndrome (ASS), inclusion body myositis (IBM), or myositis-specific autoantibody (MSA) positive myopathies, not only differentiates patients based on their clinical presentation but can also guide us to explore distinct underlying pathogenetic pathways for each group.

INITIATING EVENTS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

The rarity of IIM has made it challenging to study the initiating events that trigger the autoimmune response; however, well established epidemiological

Division of Rheumatology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

Correspondence to Eleni Tiniakou, MD, 5200 Easter Avenue, MFL Building, Center Tower, Suite 4500, Baltimore, MD 21224, USA. Tel: +1 4105506962; e-mail: etiniak1@jhmi.edu

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KEY POINTS

- The presence of additional antibodies with different specificities in patients with anti-Tif1γ dermatomyositis (DM) decreases the risk of cancer, which can affect cancer screening guidelines, adding to the hypothesis that anti-Tif1γ DM is triggered by cancer.
- Genetic alterations of the anti3-hyroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) locus can result in myopathy similar to the anti-HMGCR immune-mediated necrotizing myopathies (IMNM), and may respond to treatment with mevalonate.
- RNA sequencing from muscle biopsies of patients with antibody-specific myositis revealed transcriptomic changes similar to those caused by binding of the respective autoantibody with its autoantigen, implying a direct pathogenic role of the autoantibodies.
- Despite the prominent role of complement in muscle biopsies from patients with IMNM and in a mouse model of the disease induced by antibody transferring, a clinical trial using complement inhibitors was unsuccessful, thus implying that complement activation is an epiphenomenon.
- Mitochondrial abnormalities and oxidative stress can lead to necroptosis, upregulation of the interferon-induced genes, and potentially calcinosis, and could be reversed by repurposing *N*-acetyl-cysteine or glucagon-like peptide-1 receptor in an experimental model.

observations and genetic alterations, associated with similar clinical presentations, have provided opportunities to explore alternative investigative approaches.

Cancer as a trigger for the autoimmune response in idiopathic inflammatory myopathies

About 10–20% of patients with DM will develop cancer within 3–5 years from disease onset, suggesting a strong mechanistic relationship between the two conditions [4–6]. Nevertheless, the risk is not uniform across all types of DM; patients with anti-Tif1γ, anti-NXP2, and anti-SAE antibodies are at a higher risk [6,7]. Based on the paradigm from anti-POLR3 scleroderma, where an antitumor immune response (as indicated by POLR3-specific $CD4^+$ T cells) is initiated against a mutated POLR3 and spreads to the wild-type antigen [8], a similar mechanism could exist in myositis that potentially triggers the disease. *TRIM* loci mutations have been observed in cancer-associated dermatomyositis patients with anti-Tif1γ antibodies [9]. However, despite the strong association with cancer, only 20% of patients with Tif1γ -DM will develop clinical cancer, and the question remains as to why the rest of the patients are cancer-free [5]. Recent findings indicate that some of the cancer-free patients have concurrent autoantibodies against multiple autoantigens, with the most prevalent being the anticell division cycle and apoptosis regulator protein 1 (CCAR1) and antitranscription factor Sp4 autoantibodies [5,10–12]. This observation supports the hypothesis that: the anti-Tif1γ autoimmune response originates as an antitumor immune response and that patients with a more diversified immune response, as indicated by the presence of additional autoantibodies, are more likely to successfully prevent the progression and emergence of incipient cancer. This suggests that the combined anti-Tif1γ/CCAR1/Sp4 immune response could be explored as a potential anticancer therapy.

Insights from genetic mutations

Statins are the most commonly prescribed cholesterol-lowering medication. 10–20% of patients using statins will develop some form of toxic myopathy [13]. In rare cases, statin usage is linked to a subtype of IMNM associated with anti3-hyroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) autoantibodies [14]. These autoantibodies target the enzyme HMGCR, which is also targeted by statins [15]. A recent study reported on a subtype of limb-girdle muscular dystrophy associated with homozygous loss of function mutation of the *HMGCR* gene [16]. This study highlights two key findings: loss of function of the HMGCR enzyme results in severe, progressive myopathy that spares distal and facial muscles and is associated with elevated CPK levels, and oral supplementation of mevalonate, the end product of HMGCR, led to improvements in muscle strength. This finding was also observed in unrelated patients with an unexplained muscular dystrophy phenotype, who had bi-allelic variants in HMGCR that impaired the enzyme's activity [17]. The striking similarity between this genetic muscle disease and anti-HMGCR-positive IMNM suggests that inhibition of the HMGCR enzyme by autoantibodies could be a potential pathogenic mechanism. Although immunoglobulins have been detected in the cytoplasm of muscle fibers in anti-HMGCR+ IMNM, no distinct transcriptional changes were observed when electroporating the antibody, except for lipid accumulation [18]. If the disease mechanism indeed involves blocking the HMGCR enzyme, these studies raise the question of whether oral supplementation with mevalonate could be a viable treatment option.

Viral associations

Given the seasonal distribution of anti-MDA5+ DM, it has been postulated that viral infections could be a trigger for initiation of the autoimmune response [19–21]. Severe COVID-19 infection presented with vasculopathic manifestations resembling anti-MDA5+ DM, and findings from case reports and retrospective studies associated COVID-19 infection and vaccination with triggering anti-MDA5 immune response [22–24], possibly through sharing autoantibodies against the ACE2 receptor [25]. We have also identified an association with enterovirus infection, through the profiling of peripheral serum from patients using phage Immunoprecipitation sequencing (PhIP-Seq) against the human virome and an enterovirus library [26]. Although all these studies are limited by their retrospective design, they strongly suggest the possibility of viral triggers for autoimmune myopathies.

THE ROLE OF IMMUNE CELLS IN IIM PATHOGENESIS

T cells

Although the various forms of IIM exhibit distinct muscle biopsy characteristics, a common histological feature is muscle infiltration by T cells which are believed to play a key role in disease pathogenesis. Recent studies using T cell receptor (TCR) sequencing and RNA sequencing verified the presence of expanded TCR clones in the muscle and a shared TCR structure within and across patients [27]. Moreover, single-cell RNA sequencing of infiltrating T cells identified the expanded T cells as cytotoxic, that is, expressing granzyme B, or tissue-resident memory T cells, with shared TCR structure among the different subtypes of T cells [28]. Furthermore, the expansion of T cells in the target tissue supports the hypothesis that they likely recognize a local antigen, potentially playing a role in disease pathogenesis and flare-ups. Genetic studies still identify the HLA allele as the most significant variant associated with IIM, underscoring the critical role of T cells in the initiation and progression of the disease [29].

$CD4^+$ T cells

Effector $CD4^+$ T cells are the functional cells and help direct the immune response. Expression of TIGIT and CD226 is predominant in the circulating effector $CD4^+$ T cell population of patients with IIM, and signifies high activity [30]. Furthermore, upregulation of CD226 was also found on muscle-infiltrating T cells, the majority of which were CD4+ T cells [31]. These $CD4^+CD226^+$T cells were activated (defined as increased expression of CD69) and were located near muscle fibers that expressed CD155 (the receptor for CD226). This expression was further correlated with clinical measures of muscle damage [31], implying that these infiltrating $CD4^+$ T cells could play a role in disease pathogenesis. In juvenile DM (jDM), a significant increase in the peripheral effector Th2 $CD4^+$ T cells was observed in two independent cohorts using RNA-sequencing or multiplex Cellular indexing of transcriptomes and epitopes by sequencing (CITE-Seq) [32,33] and thought to represent T-cell dysregulation.

In contrast to effector T cells, regulatory T cells (Tregs) aim to maintain tolerance and abate an autoimmune response. In one of the above cohorts, peripheral Tregs were found to be activated and proliferative, even in untreated disease, using) [32]. These Tregs exhibited overexpression of the chemokine receptor CCR4 [32], consistent with earlier observations of skin-infiltrating $CD4^+$ T cells [34], suggesting they may be recruited to the affected skin in response to local inflammation or as a means to contribute to tissue repair.

While $CD4^+$ T cells are suggested to play an important pathogenetic role, the identity of their target antigen and whether they are the autoantigens recognized by MSAs remain unknown. These autoreactive T cells represent a very small fraction of the peripheral blood and could be missed when analyzing T cells as a whole. The presence of class-switched anti-HMGCR IgG autoantibodies and the strong association of the MHC class II allele (*HLA-DRB1∗11:01*) [35] strongly suggest the presence of HMGCR-specific $CD4^+$ T cells, which we sought to investigate. Indeed, we found that HMGCR-specific $CD4^+$ T cells were present and enriched in the Th1–17 subtype. We further honed into the exact peptides of the molecule recognized by the cells and identified shared HMGCR epitopes and common TCR motifs, allowing us to further track them in the muscle tissue, despite the rarity of T cell infiltrates in this disease [36]. This observation strongly suggests a role for antigen-specific $CD4^+$ T cells in disease pathogenesis and provides a potential avenue for highly specialized and targeted immunotherapies.

$CD8^+$ T cells

$CD8^+$ T cells are one of the main immune cells infiltrating the target muscle tissue in what has traditionally been characterized as polymyositis (PM). There are several lines of investigation supporting an active role for cytotoxic $CD8^+$ T cells (CTLs) in the IIM pathogenesis: clonal expansion of $CD8^+$ T cells in the periphery and muscle tissue of patients with IIM [37,38], indicating a targeted

immune response against a muscle antigen; perforin expression adjacent to muscle fibers, indicating activation of the CD8+ T cells [39]; the expression of Fas ligand (FasL) and inducible co-stimulatory ligand (ICOSL), ligands for receptors on CD8+ T cells, in the fibers of affected muscle [40,41]; and the upregulation of MHC class I molecules on affected muscle fibers [42]. The interaction of the $CD8^+$ T cells and the target cells can not only lead to cell death but can also release damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), that can propagate further inflammation resulting in a vicious feed-forward cycle [43,44]. A recent study showed that the muscle fibers undergo necroptosis, a type of controlled necrosis, through the interaction of the CTLs with FasL and that the inhibition of necroptosis ameliorated muscle inflammation in a murine model of PM (C-protein induced myositis, CIM) [45]. Given that the exact antigenic epitope recognized by the TCRs of these infiltrating CTLs are unknown to design targeted therapies, necroptosis inhibitors might be an effective, broad treatment option for IIM. Necroptosis was also observed in muscle biopsies from patients with DM [45,46], and there is increasing evidence that $CD8^+$ T cells could play an important role in DM as well, despite their relatively smaller numbers present in biopsies. An example highlighting the role of $CD8^+$ T cells includes the upregulation of plasma exosomes secreted predominantly by $CD8^+$ T cells and NK cells in DM patients [47]. Interestingly, these exosomes could induce autophagy *in vitro* [47], which had been previously described in DM [48,49]. Therefore, it is possible that $CD8^+$ T cells could participate in the pathogenesis of DM through multiple mechanisms and further understanding their role could enhance our knowledge of IIM pathogenesis.

B cells in myositis-specific antibody-positive Idiopathic inflammatory myopathies

Autoreactive B cells play a critical role in the pathogenesis of IIM and have garnered renewed interest as therapeutic targets. Their elimination by anti-CD19 CAR-T cells, as presented in a case series, has led to disease remission, underscoring their potential pivotal role in the disease [50]. Deep molecular and gene characterization of peripheral blood from patients with IIM (DM, ASS, jDM) have shown varying results regarding memory B cells, with increased numbers in one study on jDM [33], but decreased memory cells/increased naïve B cells in other studies on jDM and adult IIM [32,51–53]. The truth might be in between as great heterogeneity amongst patients can be seen [54].

The role of myeloid cells in Idiopathic inflammatory myopathies

Across all genome-wide association studies (GWAS) conducted in IIM, the strongest association identified was with MHC class II alleles [55–57], implicating antigen-presenting cells, such as monocytes and dendritic cells, with activating $CD4^+$ T cells. However, monocytes and dendritic cells can have additional roles in disease pathogenesis, such as the secretion of type I interferons in DM [53]. Bulk RNA sequencing of muscle biopsies from patients with DM and PM showed a positive correlation between the number of infiltrating cells and creatinine kinase (CK) raising the question about their direct role in muscle damage [58]. CITEseq on PBMCs from patients with JDM also reported on the upregulation of SIGLEC-1 on monocytes, which was thought to be a byproduct of the IFN signature and disease activity [32], and could be used as a biomarker. $CD14^+$ macrophages were also present in higher numbers in the affected skin of patients with jDM compared to juvenile lupus [59], and increased upregulation of antigen-presenting genes was found in the skin of jDM patients [60], implying a prominent role for monocytes, macrophages, and dendritic cells in disease pathogenesis.

INFLAMMATORY MEDIATORS IN IDIOPATHIC INFLAMMATORY MYOPATHY

Is idiopathic inflammatory myopathy an antibody-mediated disease?

Whether autoantibodies are pathogenic or are simply markers of the associated autoimmune response remains debated. Direct immunofluorescence on skin biopsies from patients with systemic lupus erythematosus (SLE) and systemic sclerosis showed nuclear immunoglobulin G (IgG) deposition that mirrored the ANA pattern (if the titer was sufficiently high) in very early studies [61,62]. This suggests that autoantibodies may be penetrating target tissue cells, though the possibility of an *in vitro* artifact due to tissue preparation cannot be excluded. However, the strong association of autoantibodies with specific phenotypes [3], studies reporting correlations of autoantibody titers with disease activity [63,64], and utilization of anti-CD20 agents as therapeutic options in IIM, all reignite the same question. A recent study demonstrated localization of MAS at the respective compartment, where the autoantigen is located, in patients with IIM by immunofluorescence (except for Tif1γ and NXP2). Electroporation-mediated internalization of isolated MSAs from patients into human skeletal myoblast cultures revealed transcriptomic changes

indicative of either inhibition (e.g., Mi2, PM/Scl, aminoacyl-tRNA synthetase) or activation (e.g., MDA5) of the associated autoantigens. These findings align with data from muscle biopsies for Mi2 and PM/Scl [18]. Further studies are needed to verify the penetration of the antibodies and whether binding to the autoantigen can lead to disease, but these findings can reignite the discussion on the role of antibodies in autoimmunity.

Complement activation is not the key pathogenetic mechanism in immune-mediated necrotizing myopathies

IMNM is clinically and pathologically distinct from other forms of myositis. Muscle biopsies of IMNM patients reveal necrosis, regeneration, MHC class I upregulation, and complement deposition, and the presence of IMNM is often associated with anti-SRP or anti-HMGCR autoantibodies [65]. Previous studies have demonstrated a strong correlation between anti-HMGCR or anti-SRP titers and CPK levels with an inverse relationship to muscle strength [63,64]. This has led to the hypothesis that these autoantibodies are pathogenic drivers of the disease, likely through complement activation as observed in muscle biopsies. A passive transfer mouse model supported this hypothesis confirming that treatment with complement inhibitors or using genetically modified C3-deficient mice reduced muscle weakness [66]. Consequently, a randomized, double-blinded, placebo-controlled, multicenter phase 2 clinical trial was conducted to assess the safety and efficacy of zilucoplan, a C5 inhibitor [67]. Unfortunately, the trial did not meet its primary outcome of reducing CK at 8 weeks. In conclusion, despite the substantial evidence supporting the pathogenic autoantibody hypothesis, the clinical trial failed to validate it suggesting that complement activation is probably an epiphenomenon induced by muscle necrosis. While complement activation has also been described in DM by multiple studies and verified by RNA sequencing of muscle biopsies [58], whether this mechanism is driving the disease will be verified by a clinical trial using complement inhibitors.

The role of muscle fiber death in idiopathic inflammatory myopathies and the association with the interferon signature

Oxidative stress and mitochondrial abnormalities have been observed in muscle biopsies from patients with IIM and are thought to be related to muscle inflammation [68–71]. Studies using a mouse model of $CD4^+$ T cell (Th1) dependent-myositis found that mitochondrial defects and elevated ROS production were associated with the upregulation of interferon gamma (IFNγ)-inducible genes while, on the other hand, *N*-acetyl-cysteine (NAC), a reactive oxygen species (ROS)-buffer, ameliorated the disease. This implies a central role for oxidative stress [72]. Upregulation of genes associated with oxidative stress has been demonstrated in other studies as well [58]. At the same time, ROS and mitochondrial dysfunction (as measured by PGAM5 upregulation) can also induce necroptosis (similar to the $CD8^+$ T cell-dependent CIM mouse model [45]). Therefore, it would be interesting to verify whether necroptosis was prominent in the above $CD4^+$ T cell mouse model as well. As an alternative to NAC, agonists of the glucagon-like peptide-1 receptor (GLP-1R) were also used successfully as suppressors of necroptosis [45]. GLP-1R agonists, which are common antidiabetic medications, have been found to suppress muscle wasting through the regulation of ROS and PGAM5 [73]. Consequently, GLP-1R agonists or NAC could potentially be repurposed to treat IIM.

Mitochondrial abnormalities have also been associated with type I IFN signature and, in turn, has been correlated not only with muscle damage but with increased risk for calcinosis as well in jDM. A bilateral relationship between inflammation, oxidative stress, type I IFN response, and calcified mitochondria was found and was hypothesized to be a possible explanation for calcinosis [74]. A caveat of the study is that IFNα was used while DM is a predominately IFNβ-mediated disease [75–78]. However, the observation of the bilateral relationship offers an alternative perspective on calcinosis, a condition for which effective therapies are currently lacking [75]. Supporting evidence from case report highlights the successful use of monoclonal antibodies targeting type I IFN receptors to treat calcinosis [79]; however, formal clinical trials are needed to validate these findings.

CONCLUSION

Even though major breakthroughs have been documented which have furthered our understanding of the underlying mechanisms of IIM, important questions remain unanswered. Are the autoantibodies truly pathogenic, and would their elimination effectively treat the disease? Is antibody secretion the sole function of B cells in this context, and is deletion of B cells adequate to terminate the autoimmune response? Is MHC-I and MHC-II upregulation on muscle fibers responsible for sustaining the autoimmune response through interaction with autoreactive T cells, and which autoantigens are being recognized? What are the triggers of autoimmunity

in IIM, and could we prevent the autoimmune response with vaccines? Are there shared elements of the adaptive immune system among patients with IIM that contribute to similar presentation? These are just a few of the unresolved questions that build upon the foundation of current knowledge. With advancements in artificial intelligence and the ability to study interactions at the cellular level, the future appears promising.

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Conflicts of interest

There are no conflicts of interest.

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The gut microbiota in spondyloarthritis: an update

Valeria Rios Rodriguez[a], *Morgan Essex*[a] *and Denis Poddubnyy*[a,b]

Purpose of review
This review provides an updated overview of the gut microbiota's involvement in spondyloarthritis (SpA) from a clinical perspective. It explores mechanisms by which the gut microbiota may influence SpA pathogenesis and considers the therapeutic implications of targeting the microbiome in SpA treatment.

Recent findings
The pathogenesis of SpA is multifactorial, involving genetic predisposition, external factors and dysregulation of the immune system. Recent studies have identified alterations in the gut microbiome of patients with SpA, including changes in microbial diversity and specific taxa linked to disease activity. HLA-B27 status seems to influence gut microbiota composition, potentially impacting disease progression. In HLA-B27 transgenic rats, the association between gut microbiota and SpA development has been confirmed, supporting findings from human studies. A compromised gut barrier, influenced by proteins like zonulin, may allow microbial antigens to translocate, triggering immune responses associated with SpA.

Summary
These findings highlight the potential for microbiota-modulating therapies, such as probiotics, prebiotics, diet and exercise, in managing SpA. However, methodological variability in human studies exposes the need for more rigorous research to better understand these associations. This may offer the opportunity to refine treatment strategies, offering a personalized approach to managing the disease.

Keywords
dysbiosis, microbiome, spondyloarthritis

THE GUT MICROBIOTA: AN OVERVIEW

Definition and background

The collection of symbiotic microorganisms, including bacteria, archaea, fungi, viruses, and others, that inhabit the 'body space' of a host is known as the microbiome [1]. This definition may also include the collective genomes of these microbial partners. The bacterial human gut microbiome composed primarily of species from the phyla Firmicutes (more recently renamed as Bacillota), Bacteroidetes, Actinobacteria, and Proteobacteria, plays a critical role in host health by helping with digestion, synthesizing essential nutrients, and producing short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, which have anti-inflammatory properties. The microbiome also modulates the host immune system by promoting the development of regulatory T cells and maintaining immune homeostasis [2].

The relationship between humans and microbes has evolved significantly due to pivotal scientific discoveries. In the late 19th and early 20th centuries, two distinct approaches to microbiology emerged. One, led by Robert Koch and Louis Pasteur, focused on isolating pathogenic bacteria through pure cultures, placing emphasis on identifying single causative agents of diseases. This approach undoubtedly advanced human health, as the development of antibiotics, for example, provided a powerful tool to combat many infectious diseases. However, it also led to a somewhat adversarial view of microbes, and widespread antibiotic use also had unintended adverse effects affecting the commensal bacteria in the gut. This collateral damage has been related to long-term health consequences including allergic, inflammatory diseases, as well as *Clostridioides difficile* infections [2].

[a]Department of Gastroenterology, Infectiology and Rheumatology (including Nutrition Medicine), Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany and [b]Division of Rheumatology, University of Toronto and University Health Network, Toronto, Ontario, Canada

Correspondence to Valeria Rios Rodriguez, Department of Gastroenterology, Infectiology and Rheumatology (including Nutrition Medicine), Campus Benjamin Franklin, Charité Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany. Tel: +49 30 450 514596; fax: +49 30 450 7 514 915; e-mail: valeria.rios-rodriguez@charite.de

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KEY POINTS

- This review highlights the potential to improve personalized therapeutic approaches and patient outcomes through a holistic strategy that integrates genetical predisposition, microbial dysbiosis, and environmental influences, such as diet or exercise.
- Disrupted gut barrier, driven by factors like HLA-B27 and environmental triggers, facilitates microbial translocation and immune activation, establishing the gut microbiome as a key driver of the spondyloarthritis (SpA) pathogenesis and a promising therapeutic target.
- Microbial dysbiosis in SpA, characterized by shifts in specific taxa and reduced short-chain fatty acid production, which impair gut barrier integrity, contributes to disease activity and supports the urge for development of microbiome-based therapies.
- The article underscores the need for more rigorous and well controlled research to overcome methodological challenges and enable the identification of reliable biomarkers for disease signatures and predictors.

The second school of microbiology, led by Sergei Winogradsky and Martinus Beijerinck, focused on the ecological role of microbes in nutrient cycling and environmental processes. However, this perspective began to gain recognition only toward the second half of the 20th century as the importance of microbial ecology became more apparent. Pioneering work from René Dubos further exposed the complexity of the microbiota and the concept of humans as 'holobionts', i.e. multispecies superorganisms comprised of both the host and its symbiotic microbes [3]. Together with the huge advance of genomic technologies, such as 16S ribosomal RNA (rRNA) and next-generation sequencing (NGS), the scientific community has generated a great deal of data on microbiota composition and its potential roles in health and disease, allowing to identify and study a vast array of microbial species without the need for traditional culturing methods [4] Initiatives like the Human Microbiome Project [5] have brought microbiome research into the spotlight, improving our understanding of the complex relationships between microbies and human health.

Distinct gut microbiota have been observed in several diseases, including inflammatory bowel disease (IBD) [4], obesity [6], diabetes [7], cardiovascular disease [8], autoimmune diseases such as rheumatoid arthritis [9], and cancer [10]. This phenomenon is frequently termed 'dysbiosis' to reflect an atypical or undesirable composition when compared to (healthy, disease-free) controls. In the context of spondyloarthritis (SpA), dysbiosis may contribute to disease onset and progression by altering immune responses and promoting systemic inflammation, underscoring the importance of a balanced gut microbiome for maintaining overall health and preventing chronic diseases [11▪▪].

THE GUT MICROBIOTA IN SPONDYLOARTHRITIS

The role of gut microbiome in the pathogenesis of spondyloarthritis

Human studies have shown that alterations in the gut microbiome, including changes in the microbial diversity, barrier function, and specific microbial markers, may play a crucial role in the onset, progression and management of SpA. While the exact pathogenesis of SpA remains unclear, the interaction between genetic predisposition, particularly presence of HLA-B27, barrier dysfunction and environmental factors, such as exposure to certain microbiota, may trigger immune system activation contributing to the development and persistence of the disease.

The 'leaky gut' theory suggests that specific gut bacteria or their biological matter may translocate across a compromised intestinal barrier, triggering immune responses that lead to the systemic inflammation characteristic of immune-mediated disease, such as inflammatory bowel disease (IBD) or SpA. Specifically, in SpA, the disruptions in the epithelial barrier, primarily regulated by tight junction proteins like zonulin, allow microbial antigens – including bacterial peptides, lipopolysaccharides (LPS), endotoxins, and other pro-inflammatory molecules – to trespass the gut epithelium and enter the systemic circulation. Elevated zonulin levels can lead to the malfunction of the tight junctions, increasing intestinal permeability and facilitating the translocation of these microbial products from the gut lumen into the host [12]. Once in the systemic circulation, these microbial components can activate innate immune receptors, such as Toll-like receptors (TLRs) on immune cells, resulting in the production of pro-inflammatory cytokines. In genetically predisposed individuals, such as those expressing HLA-B*27, this translocation and subsequent immune activation may drive the chronic inflammatory processes observed in SpA [13]. Clinical data support this hypothesis for the pathogenesis of SpA. Histological analyses have revealed that over 50% of patients with axial SpA exhibit microscopic gut inflammation, even in the absence of clinically apparent IBD [14]. In addition, patients with radiographic axial SpA present with elevated levels of zonulin (a biomarker indicative of

compromised gut barrier function) compared to healthy controls [15,16]. These findings suggest that a disrupted gut barrier may be a significant contributor to disease pathogenesis in SpA. However, establishing a direct causal relationship between increased intestinal permeability and the development of SpA is challenging due to the predominantly observational nature of the available studies. The variability in study methodologies, including differences in the assessment of gut permeability and the influence of confounding factors such as diet, medication, and concurrent infections, further complicates the interpretation of these findings.

Microbial dysbiosis and its implications in spondyloarthritis

Although bacterial dysbiosis has been frequently associated with SpA, the specific characteristics and implications of these alterations are unclear. Several previous reviews have attempted to gather the similarities and differences in the changes in the microbiota in patients with SpA; however, one fundamental issue is the heterogeneity of human studies. Most studies do not employ whole-genome sequencing methods, which are required to resolve bacterial species and functions, often lack statistical power, and fail to control for confounding factors such as medication use and lifestyle differences. These limitations significantly impact the robustness and reproducibility of findings, underscoring the need for well designed studies that address these variables.

Despite these challenges, certain microbial patterns seem to be identified in patients with SpA. Costello *et al.* identified a distinct microbial signature in the terminal ileum of patients with ankylosing spondylitis, speculating how dysbiosis may influence gut immunity [17]. This study observed an increase in the relative abundance of families such as Lachnospiraceae and Ruminococcaceae, which are known for their role in the metabolism of SCFAs, in line with Du *et al.* [18]. These SCFAs, particularly butyrate, are essential for maintaining the gut barrier integrity and regulating inflammatory responses by promoting the differentiation of regulatory T cells (Tregs), which help to modulate the immune response and suppress inflammation [19,20]. In addition, the study from Costello found reduced abundances of Veillonellaceae and Prevotellaceae, which may damage the gut's ability to maintain immune homeostasis [17]. Prevotellaceae are involved in the production of mucin-degrading enzymes and SCFAs [21], and their reduction could weaken the gut barrier, promoting the leaky gut phenomenon. These functional perturbations of the microbiome, such as reduced SCFA production and damaged gut barrier function, have been also associated with disease activity in SpA [22,23▪, 24,25]. However, recent literature highlights the complexity of the *Prevotella* genus, suggesting that its role may vary depending on the context, with associations to inflammatory conditions as well as to potential metabolic benefits in plant-based diets [26–28]. The shift in the microbiome science from a taxonomic description to a more functional perspective could bring some clarity in explaining how changes in microbial balance may contribute to inflammatory states.

The aim of focusing on the identification of specific taxa associated with disease activity in SpA is to discover potential biomarkers for monitoring and targeting therapy. Tito *et al.* were among the first to establish a connection between a specific bacterial genus to SpA disease activity, identifying *Dialister* as a key microbial marker with a role in driving inflammatory processes [29]. Building on this, Berland *et al.* later reported that *Dialister* and *Coprococcus* species were enriched in HLA-B27-positive individuals, where these taxa were associated with increased disease activity and elevated pro-inflammatory cytokine levels [30]. HLA-B27 is demonstrably associated with the development of axial SpA, being positive in above 90% of the cases depending on the population [31]. The findings from Berland group demonstrated that the gut microbiota not only correlates with disease activity but could also be strongly influenced by HLA-B27 status [30]. Supporting this, a recent study showed differences in the gut microbiota between HLA-B27 positive individuals with SpA and HLA-B27 positive healthy controls [32]. Although this study had a small sample size and the method used for statistical analysis (DESeq2) is not recommended for taxonomic studies in particular, [33▪▪,34] it underscores a very valid point: the necessity of including HLA-B27 positive controls in microbiota studies of SpA to accurately discern the influence of the microbiome on disease.

Building on this genetic perspective, a study by Asquith *et al.* demonstrated that specific HLA alleles, including B*27 associated with axSpA and DRB1 associated with rheumatoid arthritis, impact the gut microbiota composition, suggesting a role in the SpA pathogenesis. The study identified a notable decrease in Lachnospiraceae and an increase in the genus *Collinsella* [35]. Lachnospiraceae, which are generally beneficial for gut health due to their role in producing SCFAs, help maintain gut barrier integrity and possess anti-inflammatory properties. A reduction in Lachnospiraceae may, therefore, reduce

the ability of the gut to mitigate inflammation [36]. On the other side, *Collinsella*, is known to reduce the expression of tight junction proteins such as zonulin and occludin in enterocytes, leading to increased gut permeability. In addition, *Collinsella* upregulates the production of IL-17A, a cytokine that, while protective against infection in healthy individuals, can drive chronic inflammation in SpA through the expansion of Th17 cells [37,38]. Elevated *Collinsella* was also reported in another study comparing patients with SpA to controls with chronic back pain, underlying the close interaction between gut microbiota and genetic predisposition in the SpA development [23▪].

HLA-B27 factor and animal models to understand gut microbiome and spondyloarthritis interaction

One of the primary hypotheses exploring the role of HLA-B27 in SpA is the arthritogenic peptide hypothesis, which posits that HLA-B27 presents microbial peptides to CD8+T cells, leading to an immune response [31]. This hypothesis initially gained attention in the context of reactive arthritis (ReA), a form of SpA that occurs after gastrointestinal or genitourinary infections caused by pathogens such as Salmonella, Shigella, Campylobacter, Yersinia, and Chlamydia [39,40]. In ReA, microbial peptides resemble self-antigens through molecular mimicry, leading to cross-reactive immune responses [41]. More specifically, $CD8^+$ T cells, after recognizing these microbial peptides, may also recognize similar self-peptides, potentially triggering chronic joint inflammation. While evidence for persistent viable pathogens is limited, bacterial DNA has been detected in the synovial fluid of ReA patients, supporting this mechanism [42]. This theory emphasizes the important role that may have the gut microbiota in SpA, indicating that alterations in its composition could influence immune responses, contributing to the SpA pathogenesis.

However other theories linking HLA-B27 to disease pathogenesis are not directly related to microbes. The misfolding hypothesis, for example, suggests that HLA-B27 is prone to misfolding, which activates the stress response of endoplasmic reticulum, leading to autoinflammation through the production of pro-inflammatory cytokines (IL-17 and IL-23), while the aberrant HLA hypothesis proposes that HLA-B27 can form homodimers on the cell surface, which may be recognized by immune receptors, leading into an innate immune activation independent of the traditional antigen presentation [31]. Nevertheless, what is important to emphasize is that the presence of HLA-B27 can act as a confounding factor in studies examining the association between gut microbiota and SpA [23▪,30] and it should be considered for an accurate interpretation of microbiome data in SpA analysis.

The relevance of HLA-B27 in modulating the gut microbiome and its contribution to SpA pathogenesis has also been supported by findings from animal models. These models, which were developed decades before a medical understanding of the microbiome emerged, have recently been revisited with the focus on understanding how HLA-B27 interacts with gut microbes to influence disease development. This progression from clinical observations to experimental models offers a holistic view of how genetic factors like HLA-B27 can impact both the microbiome and disease outcomes.

Animal models displaying arthritic and colitis phenotypes, particularly HLA-B27 transgenic rats, have been crucial to understanding the role of gut microbiota in SpA. These models have demonstrated that gut microbiota is essential for the development of SpA-like symptoms. For example, when HLA-B27 transgenic rats are raised in a germ-free environment, they do not develop SpA [43]. However, when these rats are selectively recolonized with anaerobic bacteria such as *Bacteroides* spp. (and particularly *B. vulgatus*), they develop colitis and arthritis, closely mimicking human SpA [44].

Similar observations have been made in other immune-mediated disease models, such as SKG mice used to study RA [45], where the onset and disease activity are influenced by the presence of a regular gut microbiota. These findings remark the broader relevance of gut microbiota across different autoimmune disease, reinforcing the concept that the gut plays a key role in the immune modulation and disease expression [46]. Supporting this, studies in experimental SpA using different rat models, such as Lewis and Fischer rats, have shown a link between specific microbiome signatures and immune dysregulation [47].

Other animal studies suggest that the gut microbiota significantly influences immune system modulation. For example, in HLA-B27 transgenic rats, antigen-presenting cells produce less IL-10 in response to Toll-like receptor (TLR) stimulation, potentially amplifying the immune response to bacterial antigens [48]. In addition, $CD4^+$ T cells in these rats produce higher levels of interferon gamma in response to antigens from commensal gut bacteria, indicating a possible loss of tolerance to normal microbiota [49]. This dysregulated immune response may cause an imbalance between pro- and anti-inflammatory bacteria strains. These shifts in bacterial composition, depending on the rats' genetic background and environmental conditions,

may increase the prevalence of specific microbial strains associated with disease. Such is the case of *Akkermansia muciniphila* colonization in HLA-B27 transgenic rats, which correlates with the severity of the intestinal and joint inflammation, suggesting then that bacterial dysbiosis contributes to disease development [47].

In rat models that develop both arthritis and IBD, the relationship between gut inflammation and dysbiosis seems to be bidirectional. However, models where the rat develops only articular symptoms have been less explored. In this context, van Tok *et al.* investigated the role of innate immune activation by using heat-inactivated *Mycobacterium tuberculosis* in HLA-B27/Huß2m transgenic rats [46]. They found that this stimulation led to the development of spondylitis and arthritis, particularly in HLA-B27 positive rats, while controls rats did not develop the symptoms under the same conditions [46]. This amplified immune response was also associated with an increase on the production of pro-inflammatory cytokines such as TNF, IL-1, and IL-6 in response to TLR and/or dectin-1 ligands [46].

Furthermore, Gill *et al.* recently conducted a multiomics analysis to explore the interactions between microbiota changes and immune dysregulation in HLA-B27 transgenic rats with different genetic backgrounds [50], using Lewis, Fischer and Dark Agouti rat strains. They examined how genetic variation influences the relationship between gut microbiota and immune response pathways related to inflammation, such as IL-17, IL-24, and TNF. In Lewis rats, *Prevotella* and *Blautia* were strongly positive correlated with dysregulated inflammatory pathways, while *Akkermansia muciniphila* was more correlated in Fischer rats, suggesting that these taxa may drive gut inflammation differently depending on the host's genetic background. These findings show the influence of genetic background on microbiota-immune interactions, which was not evident in earlier studies that primarily focused on comparing HLA-B27 transgenic rats with wild-type controls. To overcome the limitation of 16S rRNA sequencing, which precludes any direct information into functional microbiota potential, this study also used PICRUSt analysis to predict microbial pathways associated with gut inflammation, revealing shifts in microbial functional capacity. In both Fischer and Lewis rats, this imbalance was associated with increased lipopolysaccharides biosynthesis pathways - known to exacerbate immune activation and inflammation. Metabolic pathways involved in SCFA production and steroid biosynthesis were also affected, pointing to disruptions in key processes that help maintain gut health. Specifically, the increase in SCFA production, such as butyrate and propionate biosynthesis, suggests that while these metabolites are typically protective, their upregulation in the context of inflammation might reflect a compensatory mechanism, possibly insufficient to counterbalance the ongoing immune dysregulation [50].

These results express that the functional roles of diverse microbial communities, rather than specific taxa, may be fundamental in modulating the host inflammatory response in SpA. Future studies wishing to open new routes for targeted microbiome-based therapeutic interventions, such as probiotics, prebiotics, and even fecal microbiota transplantation (FMT) will need to develop whole-metagenome sequencing and metabolomics to understand the functional differences that characterize the SpA microbiota at various disease stages.

THERAPEUTIC IMPLICATIONS

Diet and exercise

Both diet and exercise influence the gut microbiome, which could impact the progression and management of SpA. Nutritional interventions, such as diets rich in fiber, fruits, and vegetables – common in the Mediterranean diet – promote the growth of beneficial bacteria that produce SCFAs [51]. Higher intake of fiber and plant-based foods is associated with an increase of bacterial diversity in the gut microbiome, which is linked to better gut health and reduced inflammation [52,53]. Studies in RA have shown that dietary fiber, particular from whole grains and plant-based sources, plays an important role in shaping the gut microbiome composition and promoting beneficial bacteria [54]. However, the shift towards Western dietary habits – characterized by high intakes of saturated fats, sugars, and processed foods, along with lower intakes of fiber – is associated with changes in the microbiome profiles that may contribute to metabolic and inflammatory diseases [52,55]. In the context of SpA, the effects of plant-based or other restrictive diets on gut microbiota diversity and inflammation remain unexplored. This represents an interesting area for future research, as such findings could provide relevant insights into the non-pharmacological management strategies for SpA.

In addition to diet, exercise has a direct impact on the gut microbiome [56]. As a well established therapeutic strategy for managing SpA, exercise offers numerous benefits including reduced inflammation and improved physical function overall [57]. Emerging research is bringing attention to the intricate relationship between exercise, the gut microbiome and disease activity. It was recently demonstrated in genetically diverse mice that certain taxa (especially

from the Erysipelotrichaceae and Lachnospiraceae families) were able to improve motivation to exercise by activating a gut–brain axis that influences dopamine release in the brain, increasing the rewarding aspects of physical activity [58,59]. In the context of SpA, where regular physical activity is a cornerstone of disease management [57], understanding this gut-brain connection offers new potential therapeutic paths.

Promoting regular exercise, combined with a balanced and tailored diet, could help manage SpA symptoms and improve patients' motivation to stay active, which is essential for long-term disease control. Further research is needed to explore the potential of these lifestyle modifications as a nonpharmacological approach to SpA management. These interventions, together with pharmacological therapies, could reduce disease activity and promote long-term well being.

Interplay between microbiota and biologic disease-modifying anti-rheumatic drugs in spondyloarthritis

The bidirectional relationship between the gut microbiome and treatment response in SpA is becoming increasingly clear. The microbiome seems to influence not only the efficacy of conventional treatments such as sulfasalazine, but also plays a crucial role in the response to biologic therapies, including TNF inhibitors (TNFi), IL-17 inhibitors (IL-17i) and JAK inhibitors (JAKi). Studies have shown that therapeutic interventions can partially restore a healthier microbiota in patients with SpA [60]. For example, TNFi and IL-17i treatments can elevate *F. prausnitzii* levels, which correlate with reduced inflammation and improved clinical outcomes [61,62]. Additionally, TNFi therapy may increases the abundance of beneficial taxa such as Lachnospiraceae, indicating a shift towards a more balanced gut microbiome [63]. Recent findings by Lima *et al*. further highlight the influence of microbiome on treatment efficacy, demonstrating that the effectiveness of sulfasalazine responders had an enriched presence of *F. prausnitzii* and other butyrate-producing bacteria, which promoted anti-inflammatory effects [64▪].

Prebiotics, probiotics, and fecal microbiota transplant in spondyloarthritis

Recent advances in cancer treatment have revealed the potential of probiotics as adjunctive therapies, particularly in improving the efficacy and reducing the side effects of immune checkpoint inhibitors (ICIs) by modulating the gut microbiome. Studies have shown that specific probiotic strains, such as *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Bifidobacterium adolescentis*, can modulate the gut microbiome in ways that boost the immune response to ICIs, leading to better clinical outcomes in patients with melanoma [65▪▪,66]. These findings have generated expectations and interest in exploring the role of pre and probiotics and their related therapies in other immune-mediated diseases, such as IBD and SpA, where changing the gut microbiome could potentially improve the treatment outcomes.

Probiotics, which involve the administration of live beneficial bacteria in adequate quantities, have thus far been poorly studied as a strategy to modulate the gut microbiome in patients with SpA. To date, there are only two studies that have investigated their effectiveness in SpA, presenting meager results. An internet-based study in 2008 did not find clear improvements in disease activity or patient well being [67]. Similar results were reported shortly after in a randomized clinical trial, which showed no clear improvements in disease activity among patients with SpA who received *Streptococcus salivarius, Bifidobacterium lactis*, and *Lactobacillus acidophilus* in comparison with placebo [68]. The lack of strain- or even species-level resolution in microbiome SpA studies is one of the major reasons probiotic clinical trials have not been able to advance.

Prebiotics, defined as nondigestible food ingredients that stimulate the growth of beneficial bacteria in the gut, are another area of interest. Compounds like inulin and fructooligosaccharides support the growth of bacteria producers of SCFA such as *Faecalibacterium prausnitzii*, which are known for their anti-inflammatory effects. While prebiotics have demonstrated benefits in other inflammatory and gut-related conditions [69], there is currently no direct evidence from studies specifically addressing their effects in SpA.

Fecal microbiota transplant (FMT) is a highly effective method to restore gut microbial diversity by transferring feces from a healthy donor to a recipient [70]. This approach has revolutionized the treatment of recurrent *Clostridiodes difficile* infections (rCDI), where the use of antibiotics provokes a loss of colonization resistance, allowing C. difficile overgrowth. The toxins produced by *C. difficile* result in gastrointestinal symptoms, provoking inflammation which can impact quality of life of the host. FMT has shown success in reintroducing beneficial bacteria, helping to reestablish the natural resistance of the gut to C. difficile. Two microbiota-based therapies, Rebyota and CP101, have been recently approved by FDA for rCDI, with clinical trials demonstrating their ability to restore microbial diversity and prevent infection recurrence

[71]. However, its efficacy in treating extraintestinal immune-mediated diseases like SpA remains unclear. A recent exploratory randomized clinical trial assessed FMT in patients with active peripheral psoriatic arthritis. Unexpectedly, the study found that FMT was inferior to placebo in reducing disease activity, raising fundamental questions about the gut-joint axis and the role of dysbiosis in SpA pathogenesis [72,73▪▪]. While FMT showed no serious adverse events, the findings suggested the need for further studies to better understand the mechanisms at play and refine the use of FMT in SpA.

CONCLUSION

As our understanding of the role of gut microbiome in SpA deepens, future research will most likely focus on refining microbiome-targeted therapies. The complex interactions between genetic predispositions, microbial dysbiosis, and environmental factors suggest that a holistic approach to treatment – considering the gut as a key player in the SpA pathogenesis – could set up an imprint in patient outcomes improvement.

Moving forward, the integration of microbiome-modulating strategies such as lifestyle modifications, pre/probiotics, and FMT with existing treatments offers an alternative direction for SpA management. We need to keep in mind that current evidence is still in its early stages, and further research is needed to better understand these therapies' mechanisms and their clinical applications. Randomized, large-scale, well designed clinical trials are crucial to identify specific microbial signatures that could serve as biomarkers for disease activity or treatments response, directing towards a more personalized approach, and ultimately transforming the landscape of SpA management.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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