# 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

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Dr Polly Ferguson received her B.S. and M.D. from the University of Iowa. She completed her Pediatric Residency and Pediatric Rheumatology & Immunology Fellowship and Post-Doctoral Research Fellowship at the University of Virginia. She is currently the Marjorie K. Lamb Professor of Pediatrics and Director of Pediatric Rheumatology at the University of Iowa Carver College of Medicine. She is an NIH funded investigator and her research program is focused on the etiology of autoinflammatory disorders including chronic recurrent multifocal osteomyelitis (CRMO) and neuroinflammation. She is an author on more than 100 peer reviewed publications, book chapters and reviews. Her work has been cited more than 5000 times.

# Treatment of juvenile localized scleroderma: current recommendations, response factors, and potential alternative treatments

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**Purpose of review**
Juvenile localized scleroderma (jLS) is a chronic autoimmune and fibrosing disease associated with a high risk for functional impairment. Antifibrotic options are limited, so current treatment strategies are focused on disease activity control. Pediatric rheumatologists are in consensus on the need to treat with systemic immunosuppressants, in particular, methotrexate. However, more than 30% of patients fail initial methotrexate treatment. This review provides an update on current management and reviews reports on potential alternative treatments.

**Recent findings**
An overview of current treatment recommendations and its efficacy are discussed. Recent studies have identified several factors associated with likelihood of treatment response. These include time to initiation of treatment, certain subtypes, and extracutaneous involvement. Findings from recent reports of alternative systemic immunomodulators, including biologic medications, will be summarized.

**Summary**
Methotrexate treatment has greatly improved outcome for most jLS patients but a substantial portion have refractory cutaneous and/or extracutaneous disease. Treatment response factors are being identified, which could lead to improved management strategies. Recent studies provide further support on mycophenolate mofetil as an alternative treatment. Data on biologic therapies is encouraging, with data suggesting efficacy for many extracutaneous manifestations but more studies are needed to evaluate these and other options for jLS.

**Keywords**
biologics, localized scleroderma, morphea, refractory disease, treatment

## INTRODUCTION

Localized scleroderma, also called morphea, is a chronic, autoimmune, and fibrosing disease that presents in different patterns known as subtypes (circumscribed, linear, generalized, pansclerotic, and mixed). T-cell patterns have been found altered in localized scleroderma, with elevated levels of TH1/IFNγ-related chemokines and decreases in TH17-associated cytokines identified in the skin [1▪]. The inflammatory phase appears associated with TH1/IFNγ predominance, whereas the fibrotic phase is dominated by TH2 [1▪]. Juvenile-onset localized scleroderma (jLS) is associated with poorer outcome than adult-onset (aLS) disease, largely related to the higher frequency of deep, including extracutaneous, involvement in jLS [2]. In recent studies, the majority of jLS patients have been found to have extracutaneous involvement (ECI) most commonly musculoskeletal [3▪]. Musculoskeletal morbidities include arthritis, tenosynovitis, contractures, myositis, and bone growth impairment. Patients with craniofacial disease are at higher risk for ocular, oral, and neurological problems including uveitis, dental problems, seizures, and movement disorders [4▪].

Treatment for jLS depends upon the disease pattern, with disease activity status and risk for poor outcome the main considerations (Table 1). Most

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## KEY POINTS

- Systemic immunosuppressants are recommended for treating active juvenile localized scleroderma patients at risk for moderate-to-severe morbidity.
- Methotrexate is recommended by pediatric rheumatologists and the 2019 Cochrane review, and is effective in ~66 to 67% of patients.
- Potential risk factors for methotrexate nonresponse include certain subtypes (pansclerotic, mixed morphea, linear of limb), extracutaneous involvement, and a delay in treatment initiation.
- Mycophenolate mofetil is recommended for treatment of patients that are refractory to or intolerant of methotrexate.
- More work is needed to further evaluate other treatments, with biologic agents abatacept and tocilizumab appearing promising options especially for those with extracutaneous involvement.

current treatments are effective against inflammation not fibrosis, so therapy is directed towards controlling disease activity to minimize the risk for damage. Therapy for patients with inactive disease is focused on improving or maintaining function through physical and occupational therapy, and skin care. Patients with active disease and a low risk for poor outcome can be treated with topical agents and/or phototherapy. These treatments are insufficient for patients with active disease and a moderate-to-high morbidity risk who need systemic immunosuppressives to ensure adequate targeting of tissues deeper than the dermis, as was stated in a recent Cochrane review on morphea treatment [5▪]. This review is focused on providing an update on treatment of patients needing systemic treatment, the patients most commonly seen by the rheumatologist. None of the medications discussed in this review are Food and Drug Administration (FDA)-approved for use in jLS.

The Pediatric Rheumatology European Society (PRES) and Children's Arthritis and Rheumatology Research Alliance (CARRA, a North American pediatric rheumatology research network) are in agreement on the use of methotrexate (MTX) to treat jLS patients with active disease who are at moderate-to-high risk for poor outcome. Each organization developed regimens based upon best available data and their members' preferences (Fig. 1) [6▪▪,7]. Although PRES recommends an initial 3 months of concurrent corticosteroid treatment with MTX, the CARRA group developed three MTX-based standardized regimens called consensus treatment plans (CTPs) that differ based on inclusion and type of corticosteroid treatment as they thought data insufficient to recommend a single regimen (Fig. 1). The intention is that the CTPs should be studied in comparative effectiveness studies to determine relative efficacy enabling iterative work towards identifying optimal care. The 2019 Cochrane review of the literature supports the use of methotrexate treatment for jLS patients with active localized scleroderma although considers

**Table 1.** Indications for systemic immunosuppressive treatment of juvenile localized scleroderma

| Signs of active disease | | Factors associated with moderate-to-high morbidity risk | |
|---|---|---|---|
| **Cutaneous** | **Extracutaneous** | **Subtypes** | **Other factors** |
| Erythema | Arthritis | Circumscribed deep morphea | Lesion located on the head, or in a cosmetically sensitive area |
| Violaceous, lilac, bruise-like | Tenosynovitis | Linear scleroderma | Lesions crossing a joint |
| White or yellow waxy lesion: abnormal skin texture, associated with skin thickening | Myositis | Generalized morphea | Extensive disease |
| | Fasciitis | Pansclerotic morphea | Rapidly progressive disease |
| | Uveitis | Mixed morphea | Extracutaneous involvement |
| Skin thickening | Potential activity signs: new or worsening headaches, migraines, seizures, arthralgia, myalgia, spasm or neuropathy, growth disturbances | | |
| Tactile warmth | | | |
| New or worsening hair loss on scalp or face | | | |
| Disease extension: new or larger lesion with one or more of above features, or deeper lesion | | | |

Systemic immunosuppressive treatment is indicated for juvenile localized scleroderma (jLS) patients with active disease who are at risk for moderate-to-severe morbidity. This table is derived from active disease and inclusion criteria developed by CARRA for treatment studies [4▪]. Skin thickening and tactile warmth need to be assessed in comparison to the unaffected, ideally contralateral site, and skin thickening alone is not specific for activity [5▪]. One of the challenges of identifying disease activity in jLS is that some morbidity features, such as headaches, seizures, and arthralgia, could reflect damage from prior inflammation versus potential continued activity in addition to damage. Imaging studies and sometimes biopsies may be needed to determine the disease state.

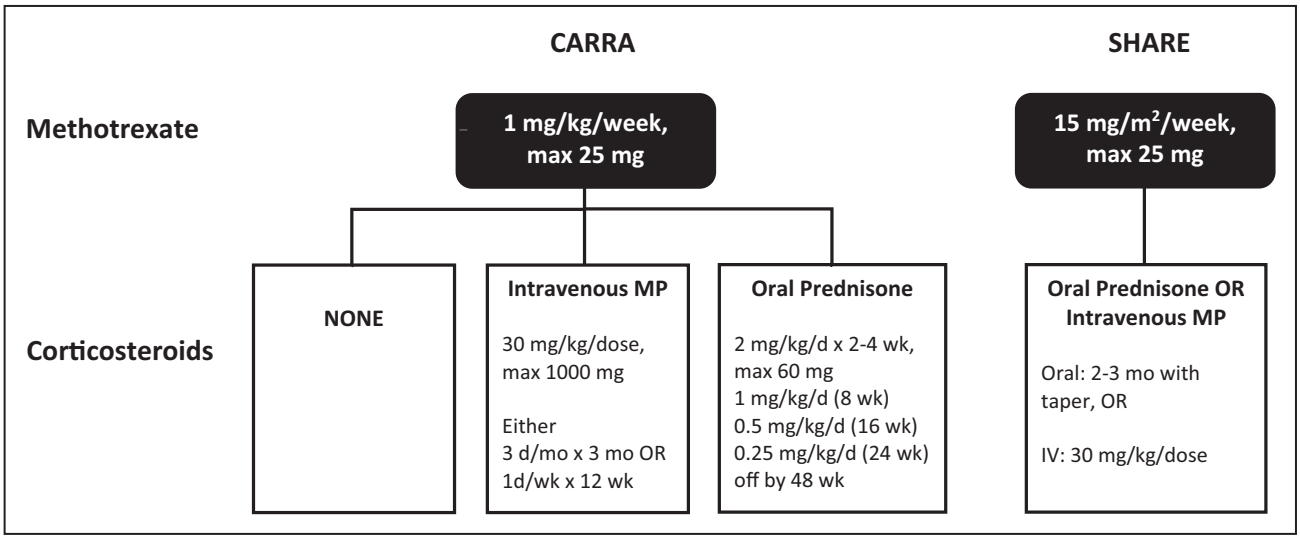


**FIGURE 1.** Methotrexate treatment recommendations from pediatric rheumatology organizations. Members of the Pediatric Rheumatology European Society (PRES) developed consensus-based recommendations for jLS treatment as part of their Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) project [7]. The Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American pediatric rheumatology research network, developed three methotrexate-based consensus treatment regimens known as consensus treatment plans (CTPs) based upon current treatment practices of their members and best available evidence [8]. The intention was that these CTPs should be studied in comparative effectiveness studies to determine relative efficacy and tolerability to work towards identifying 'best' treatments. D, day; jLS, juvenile localized scleroderma; kg, kilogram; Max, maximum; mg, milligrams; mo, month; mp, methylprednisolone; wk, week.

the evidence of low quality, related to small sample size and unclear risk of selection bias [5▪].

The widespread adoption of MTX treatment of jLS by pediatric rheumatology has led to major improvements in occurrence of joint involvement (50% pre-MTX to current 23%) and limb length hemiatrophy (23% pre-MTX to current 9%) [4▪]. Even more striking is the reduction in orthopedic surgeries, from 41% pre-MTX, including 5% amputations, to current 14% surgeries without amputations [4▪]. Unfortunately, two prospective studies have shown a substantial minority fail to respond to MTX. In the MTX double-blind, placebo-controlled, randomized clinical trial (RCT) of 70 jLS patients, 67.4% of those on MTX maintained disease inactivity after an initial 3 months of prednisone compared with 29.2% in the placebo arm [8]. A CARRA pilot CTP feasibility study evaluating response to CTP treatment in 50 jLS patients found 33 to be responders, 11 treatment failures, and 6 dropped out of study, yielding an overall response rate of 66% [9▪].

## FACTORS ASSOCIATED WITH POORER RESPONSE TO TREATMENT

Identifying patients less likely to respond to MTX potentially could improve outcome, by enabling earlier identification of patients who need to change treatment or better treatment strategies. Several studies have implicated specific subtypes in likelihood of response. Although the rarity of pansclerotic morphea has precluded studies on treatment response, many case studies report pansclerotic morphea to be refractory to MTX and many other treatments [10]. Circumscribed morphea was associated with a higher likelihood for a good MTX response than other subtypes in two studies [9▪,11]. In contrast, mixed morphea was associated with treatment failure in the pilot CTP study [9▪], and higher relapse rates in two other studies [12,13]. One of these studies found relapse risk to be associated with linear scleroderma of the limb, either solitary or as part of mixed morphea [13]. However, studies from Zulian and Martini's group have not found any subtype-related difference for likelihood of remission or relapse [14,15].

As is true for inflammatory arthritis, earlier initiation of treatment in localized scleroderma is associated with improved response, with higher likelihood for remission and lower risk for relapse [11,14]. A study of 126 jLS patients found a delay of 79 days in treatment initiation (144 vs. 65 days) significantly affected remission likelihood ($P = 0.001$) [14]. Sex has not been found associated with treatment response, and age of disease onset was also not found associated [9▪,16].

Extracutaneous involvement (ECI) was found associated with treatment failure in the CTP study

[9▪]. Another prospective study suggests possible reasons for this relationship. Patient with ECI were found to have greater skin disease extent ($P < 0.001$), indicating they had an overall greater disease burden than patients without ECI [3▪]. Patients with ECI had a smaller decline in physician global assessment of disease activity (PGA-A) scores over time than those without ECI, despite being more frequently treated with MTX and corticosteroid, suggesting a poorer response to treatment in the patients with ECI ($P = 0.021$) [3▪].

Specific extracutaneous problems, such as arthritis and arthropathy, have also be found less responsive to MTX treatment than skin disease. Among four studies reporting on 25 jLS patients with arthritis and fibrous arthropathy, over 75% received additional medications, with joint disease still refractory in 32% [17▪,18–20]. In another study, muscle involvement was present in 39% and bone growth impairment in 26% of patients despite more than 80% of the patients having received or receiving MTX and corticosteroid treatment [3▪]. Another study identified myopathy in eight of nine patients after MTX treatment [21]. MTX treatment has ameliorated neurological problems, such as neuropathy, headaches, migraines, and hemiparesis in some but not all patients [22–24], with other problems, such as seizures and neuropsychiatric problems often refractory [25,26▪,27].

## WHEN TO CONSIDER NONRESPONSE TO INITIAL MTX TREATMENT?

Two recent studies reported similar time course responses to MTX, as shown in Fig. 2. Most of the improvement in skin response occurs in the first 3 months, with response expected by 6 months [28,29▪]. So, a change in the treatment regimen should be considered if the patient worsens at 3 months or fails to improve by 6 months.

## STRATEGIES FOR PATIENTS WHO FLARE OR ARE NONRESPONDERS

Longer course of MTX used with additional corticosteroid treatment was found to improve response in a long-term follow-up of jLS patients who had participated in the initial MTX RCT. Fifteen of the 46 patients in the MTX arm flared by the end of the 1-year trial. They received an additional 3-month course of prednisone (1 mg/kg/day × 2 months, then tapered), and were followed with the MTX responders and 19 of the patients in the placebo arm that had flared or been nonresponders. Placebo nonresponders were treated with MTX and 3 months of prednisone too. At a mean duration of 3.4 years, 74% of the patients were in remission, including 54% off MTX [16]. Only 15% were refractory, an improvement over the 33% nonresponse rate found at the end of the 1-year RCT [8,16]. An even longer term follow-up study

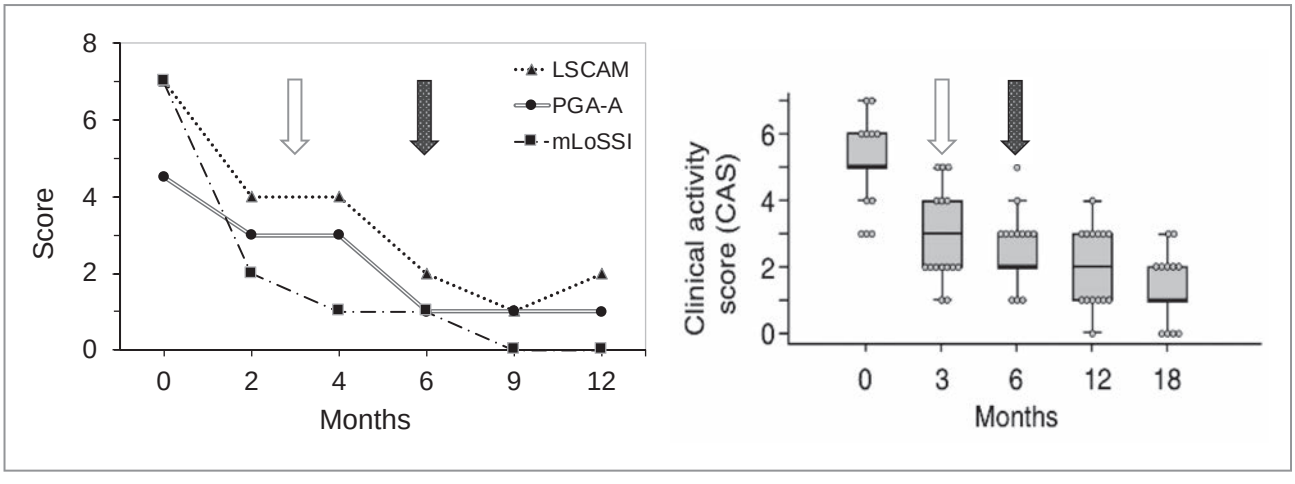


**FIGURE 2.** Time course of response to methotrexate treatment. The time course of activity response in two prospective studies of jLS patients beginning methotrexate treatment is shown. Much of the improvement occurs in the first 3 months (white arrows), with nearly all of the improvement occurring by 6 months (dark arrows). (a) The median scores for Physician global assessment of disease activity (PGA-A) and two skin activity measures [modified Localized Skin severity index (mLoSSI), Localized Scleroderma Cutaneous Activity Measure (LSCAM)] for 44 jLS patients initiating treatment with one of the three methotrexate-based consensus treatment plans (CTPs) [10,27]. One CTP did not include concomitant corticosteroid treatment, the others included either prednisone tapered off by 48 weeks or intravenous methylprednisolone for the first 12 weeks. (b) Boxplots of the clinical activity score for 22 jLS patients beginning methotrexate and corticosteroid treatment are shown. The clinical activity score assesses skin tightness, erythema, disease extension, and atrophy in a single lesion, with the same lesion tracked over time. Reproduced with permission from Weibel *et al.* [29▪].

by the same authors of 47 jLS patients treated with MTX reported all patients were in remission at end of 9-year follow-up [30▪]. Relapses occurred in 23% of the patients during follow-up; while authors did not say, they likely were treated with prednisone, similar to flare patients in earlier study.

## POTENTIAL ALTERNATIVE TREATMENT OPTIONS

Several recent studies have reported on use of alternative systemic medications to treat localized scleroderma. As most of the studies have been small retrospective case series, data is very limited for most of the medications discussed in this section. In addition, studies varied in the evaluations and scoring metrics used to assess outcome, limiting cross study comparisons.

## MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) has wide support among pediatric rheumatologists as a treatment for the MTX nonresponder [7]. PRES recommended MMF as the next systemic immunosuppressant treatment for patients refractory to or intolerant of MTX [6▪▪], and the CARRA LS workgroup developed CTPs for MMF [7]. Use of MMF for localized scleroderma is supported by the demonstration of its efficacy in reducing skin thickening in systemic sclerosis RCTs [31]. In addition, analysis of skin biopsy samples from patients in one of these trials showed a decrease in the inflammatory gene signature, the signature shared with localized scleroderma [32,33].

Table 2 provides two recent MMF case series, one of jLS, the other of aLS [30▪,34▪]. Most received MMF because of an inadequate response to prior treatment, and these patients had a higher frequency of the more extensive, and/or severe subtypes (pansclerotic morphea, mixed morphea, and generalized morphea). The jLS patients had all previously been treated with MTX and CS, and many continued on these medications with MMF. The majority of patients improved, with 35% of adults and 91% of jLS in remission at last follow-up (13.5 months, 9.4 years, respectively). Although 46% of jLS patients relapsed at a mean time of 31 months, most still achieved disease control, with 50% able to remain in remission off MMF at last follow-up [30▪]. Studies reported a 10–55% frequency of adverse events but this rarely led to discontinuation of MMF (0–16%).

## OTHER SYNTHETIC MOLECULES

Since 2019, here have been three reports on other synthetic molecules used to treat localized scleroderma (Table 2). A case report on cyclosporine A (CSA) included only one jLS patient, so findings from this and a 2016 study on 12 jLS and aLS patients [35,36] were collated. Patients were treated with CSA because of an inadequate response to prior treatment; more than 30% had pansclerotic morphea or generalized morphea. Nearly all patients had at least a partial response in the first 2 months, and 38.5% were rated as in remission at last follow-up (10 months to 10 years). However, 38% of patients relapsed and 46% had an adverse event, including known serious adverse events associated with CSA (elevated creatinine, elevated transaminases, hypertension). Adverse events limited the dose and/or duration of CSA treatment.

A retrospective review of 84 localized scleroderma patients treated with hydroxychloroquine as their first systemic medication found most (81%) patients had at least a 50% level of improvement, with remission in 43% [37]. Relapses occurred in 13%, and adverse events were low (Table 2). However, the high rate of response partly reflects the high frequency of circumscribed morphea patients in this cohort (35%), with patients with this subtype found to have a 97% response rate compared with 64% for those with linear scleroderma [37]. So data does not support the use of hydroxychloroquine as solo rescue treatment for MTX nonresponders. Hydroxychloroquine might be used as adjunctive therapy in combination with another disease modifying antirheumatic drug (DMARD) for nonresponders but more study is needed to evaluate that approach.

Two studies have evaluated Janus Kinase inhibitors (JAKI) treatment in a total of five aLS and one jLS patients. All of the aLS patients had generalized morphea, with one also having this with deep morphea [38▪], whereas the jLS patient had pansclerotic morphea [10]. Four patients received tofacitinib, dose 5–10 mg twice daily, one received baricitinib 2 mg per day, and the jLS patient received ruxolitinib (dose not specified) [10,38▪]. All five aLS patients were said to show meaningful improvement by 5–9 months [38▪], whereas the jLS patient failed to respond [10]. Prior treatment included methotrexate [4▪], mycophenolate mofetil [2], corticosteroids [5▪], and extracorporeal photopheresis [2]. The jLS patient with pansclerotic morphea had previously failed treatment with intravenous pulse methylprednisolone, intravenous immunoglobulins, hydroxychloroquine, rituximab, and tocilizumab, and eventually underwent hematopoietic stem cell transplant [10]. One of the aLS patient

**Table 2.** Other disease-modifying antirheumatic drug and biologic treatment of juvenile localized scleroderma

| | MMF [30▪] | MMF [34▪] | CSA [35,36] | HCQ [37] | JAKI [10,38▪] | Abatacept [41,42▪] | Tocilizumab [10,26▪,43--48] | Infliximab [39,40] |
|---|---|---|---|---|---|---|---|---|
| Number of Patients | 22 jLS | 77 aLS | 13: 4 jLS, 9 aLS | 84: 34 jLS, 50 aLS | 5 aLS<br>1 jLS | 26 jLS | 24 jLS | 2: 1 jLS, 1 aLS |
| Reason for drug:<br>Inadequate response | 95.5%: prior rx 100% MTX and CS | 65%: prior rx 70% MTX: NS CS, HCQ | 100%: prior rx 23% MTX, 61.5% CS; 31% PUVA | 0 | 100%: prior rx 67% MTX, 33% MMF, 83% CS, 33% ECP/PUVA<br>17% biologic (1 toci, ritux, IVIG) | 88.5%: prior rx 92% MTX and/or MMF, 100% CS, 8% HCQ, 4% biologic (2 TNFi, 1 toci) | 100%: prior 100% MTX and/or MMF, 13/13 CS, 21% biologic (3 TNFi, aba, 2 ritux), 1 CYC, 1 plasmapharesis | 100%: prior 100% MTX, 50% MMF, 50% CS, 50% HCQ |
| Intolerance<br>Initial rx | 4.5%<br>0 | 27%<br>16% | NS<br>8% | 0<br>100% | 0<br>0 | 19%<br>0 | 5%<br>0 | 50%<br>0 |
| Subtype | Circ 5%<br>Linear 36%<br>GM 9%<br>Panscl 18%<br>Mixed 32% | Circ 9%<br>Linear 20%<br>GM 48%<br>Panscl 16%<br>Mixed 8% | Circ 8%<br>Linear 23%<br>GM 38.5%<br>Panscl 31%<br>Mixed 0 | Circ 35%<br>Linear 35%<br>GM 17%<br>Deep 12%<br>Mixed 2% | Circ 0<br>Linear 0<br>GM 67%<br>Panscl 17% (jLS)<br>Mixed 17%: GM and deep | Circ 4%<br>Linear 54%<br>GM 11.5%<br>Panscl 0<br>Mixed 31% | Circ 4%<br>Linear 52%<br>GM 0%<br>Panscl 30.4%<br>Mixed 13%: includes 1 panscl | Circ 0<br>Linear 0<br>GM 50%<br>Panscl 0<br>Mixed 50%: GM and linear |
| ECI and/or functional impairment | 14%; 2 dental, 1 MRI abnormality | 53%; 21 joint, 1 LLD, 7 arthralgia/ pain, 10 neuropathy, 5 HA, 2 anxiety/ depression, 1 vision | 38.5%; 4 joints, 1 migraine and dental | 13%; 7 joints, 2 seizures | 50% joints, 17% ulcers | 65%: 14 joint, 2 neuropathy (orofacial, limb), 1 HA, 1 seizure | 73%; 7 joint, 7 LLD, 2 FHA, 2 uveitis, 1 sz, 2 MRI brain abnormality | 50%; 1 joint |
| Dose of medication | 700–1000 mg/ $m^2$/day | 27% at least 3 g/day<br>49% 2--2.9 g/day<br>20% 1--1.9 g/day<br>4% <1 g/day | 2.4 or 3 mg/kg/ day | 5 mg/kg/day, adults 400 mg | Tofacitinib 5–10 mg b.i. d., baricitinib 2 mg daily, or ruloxitinib: dose not specified | 10 mg/kg/dose i.v. or SC by JIA dosing | 8--12 mg/kg/dose i. v. at 2–4-week intervals, or SC by JIA dosing | 5 or 10 mg/kg/dose i.v. q 4 week |
| Concurrent DMARD<br>CS | 54.5%<br>NS | 30%<br>49% | 0<br>31% | 0<br>0 | Min 67%<br>Min 33% | 100%<br>81% | 65%<br>43% | 50%<br>0 |
| Response: % improved | 91% | 60.3% at 3–6 mo; 61% at 9–12 mo | 92% (46% partial) | 81% at least 50% | 83% | 88.5% | 78% | 100% |
| Time to improvement or evaluated | 39.5 mo | 3–6 mo | 1–2 mo for most | 4 mo; 12 mo max | 1--3 mo initial,<br>5--9 mo to clinical meaningful change | >50% by 6 mo, response by 12 mo | 21% said rapid, some by 3 mo | 2--3 mo |
| Response: remission | 91% remission, 50% off MMF | 13% at 9–12 months<br>35% end of study<br>22% off MMF | 38.5% | 43% initial; 30% without relapses | 83% stably improved or controlled; 17% off JAKI | 75% minimum at 11–12 months<br>61% at 24 months | 53–74% | 50% |

**Table 2** (*Continued*)

| | MMF [30▪] | MMF [34▪] | CSA [35,36] | HCQ [37] | JAKI [10,38▪] | Abatacept [41,42▪] | Tocilizumab [10,26▪,43--48] | Infliximab [39,40] |
|---|---|---|---|---|---|---|---|---|
| Time remission assessed | 9.4 years | 13.5 months | 10 months to 10 years | 14.5 months | 4–16 months; follow-up 10–40 months | 11–12 months | 9–31 months | 5 months |
| ECI improvement | Not reported | Not reported | Minimum 60% of those with ECI: 2 joints, 1 migraines | Not reported | 67% of those with ECI (2/3); 2 joint, 1 ulcer | 71% of those with ECI (13/17); 12/14 of joint/muscle, 1 orofacial pain, 2 neuropathy | 31.5% of those with ECI (6/19): 3 arthritis, 1 seizure, 1 uveitis, 1 periodontal edema and dysphagia, 2 MRI imaging abnormality | 100% in 1 pt that had joint |
| Adverse events | 55%, 0 DC<br>23% HA, 18% LFT, 9% GI, 9% fatigue | 44%, 16% DC<br>31% GI, 4% cytopenia, 3% infection | 46%, estimate 15% DC. LFTs, ↑wt, ↑ Cr, HTN. 1 pt hepatic cell cancer | 12%, 0 DC<br>Mainly GI | 0 | 17%, all DC<br>Mood/behavioral changes | 4%, 0 DC<br>pneumonia | 50%, 0 DC<br>Herpetic lesion |

Recent studies on alternative systemic treatments for jLS are shown. Prior biologic treatment for abatacept were adalimumab, inflixiximab, and tocilizumab, and for tocilizumab were etanercept (three patients) and abatacept. For tocilizumab, prior corticosteroid treatment was not specified for 11 of the patients. Aba, abatacept; aLS, adult onset localized scleroderma; b.i.d., two times per day; circ, circumscribed morphea; Cr, serum creatine; CS, corticosteroid; CSA, cyclosporine A; CYC, cyclophosphamide; DC, discontinued medication; DMARD, disease modifying antirheumatic drug; ECI, extracutaneous involvement; FHA, facial hemiatrophy; GI, gastrointestinal symptoms, such as nausea, vomiting, abdominal pain; GM, generalized morphea; HA, headache; HCQ, hydroxychloroquine; HTN, hypertension; i.v., intravenous; IVIG, intravenous immunoglobulin; JAKI, Janus Kinase Inhibitor; JIA, juvenile idiopathic arthritis; jLS, juvenile onset localized scleroderma; LFT, liver function tests; linear, linear scleroderma; LLD, limb length difference; max, maximum; mg, milligrams; min, minimum; mixed, mixed morphea; MMF, mycophenolate mofetil or myfortic; mo, month; MTX, methotrexate; NS, not specified; panscl, pansclerotic morphea; PUVA, psoralen and ultraviolet A; ritux, rituximab; rx, treatment; s.c., subcutaneous; TNFi, tumor necrosis factor inhibitor; Toci, tocilizumab; wt, weight.

relapsed when tofacitinib was tapered, with control regained after drug resumption. No adverse events were found.

## BIOLOGIC TREATMENTS

Several case series have reported on the use of biologics for refractory jLS, most commonly abatacept and tocilizumab [10,26▪,27,39–41,42▪,43–48]. Recent SSc trials suggest benefit for both these treatments, with abatacept found beneficial in patients who had the inflammatory skin gene expression that is shared with localized scleroderma [49], and tocilizumab treatment associated with a trend towards improved skin scores and lung function stabilization [50]. There have also been aLS case reports of benefit from abatacept [51–53].

Nearly all biologic-treated jLS patients had failed prior treatment with MTX and/or MMF, usually given with CS. A few patients had failed other biologics, most commonly TNFi. As expected, these patients had higher percentage of more severe disease, including more extensive linear scleroderma, and higher frequency of pansclerotic morphea, generalized morphea, and/or mixed morphea (Table 2).

Dosing of the biologics generally followed JIA recommendations with most patients receiving intravenous dosing for abatacept and tocilizumab. All the abatacept-treated patients received concurrent DMARD treatment, compared with about half the patients treated with tocilizumab or infliximab. Encouragingly, 78–100% of the patients improved with biologic treatment, despite many having had prolonged treatment with several other systemic immunosuppressants. Among the studies that reported on the time course, many patients improved in the first 6 months. Remission was hard to judge in most of the studies; more detail was provided for one of the abatacept and one of the tocilizumab studies where skin scores and physician assessments were reported at 6-month intervals [42▪,45]. These two studies also reported more clearly on relapses, which occurred 1–2 years after treatment initiation. The biologics were generally well tolerated, with a low frequency of adverse events, so more study of this class of medications is warranted.

The biologics and JAKI also appear effective against musculoskeletal ECI (Table 2). Among those with joint involvement, 12 of the 14 abatacept treated, all 3 of the tocilizumab treated, 2 of the 3 JAKI-treated, and the 1 infliximab-treated patients improved. Abatacept and tocilizumab may also improve some other types of ECI (Table 2). Two tocilizumab case reports described a reduction or cessation of seizures, with one of these patients also having resolution of uveitis, and the other improvement in her cognitive function and altered personality; both of these patients also had improvement in their brain MRI scans [26▪,27]. Another patient with craniofacial localized scleroderma associated with growth defects of mandible and nose, periodontal bone edema, dental root resorption with tooth loss, and oral pain and dysphagia, had resolution of the periodontal bone edema on MRI, oral pain, and dysphagia after 6 months of tocilizumab treatment [47].

## CONCLUSION

Advances in the treatment strategy over the past two decades have greatly improved jLS outcomes, with a reduction of severe morbidity and the need for corrective surgery. Pediatric rheumatologists are in consensus on the use of methotrexate to treat active disease in patients at risk for poor outcome. However, a third of patients have an inadequate response to methotrexate, and 27% of jLS patients still have functional impairment. Recent studies have identified potential factors associated with poor response that may lead to rational personalized treatment approaches in the future. Recent scleroderma studies support the use of mycophenolate mofetil for localized scleroderma patients refractory to methotrexate treatment. Initial studies are encouraging on the potential role of abatacept, tocilizumab, and JAKI as additional treatment options, including for ameliorating extracutaneous manifestations. As extracutaneous involvement is prevalent in jLS, it is important that future studies evaluate treatment efficacy on all disease manifestations. Advances in our understanding of pathophysiology offer hope for identifying additional well tolerated and effective treatments to work towards eliminating functional impairment and disfigurement.

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### Conflicts of interest

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# Not all benign: disease course, complications, and sequalae of chronic recurrent multifocal osteomyelitis in children

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**Purpose of review**
Advances in pathogenesis of chronic recurrent multifocal osteomyelitis in children (CRMO) have shaped therapeutic strategies. The use of whole-body MRI (WBMRI) and improved awareness of CRMO has increased rates and timeliness of CRMO diagnoses. In this review, we highlight the findings from recently published CRMO cohorts and describe the course, complications, and long-term sequalae of CRMO. It is important for clinicians to be aware of the potential for long-term sequelae in order to optimize therapy and avoid complications.

**Recent findings**
Despite recent advances in defining disease pathogenesis, children with CRMO continue to suffer from complications and deformities. Involvement of the spine can be asymptomatic and is not as rare as previously suggested. This can result in damaging outcomes, such as vertebral fractures and permanent deformities. A subset of patients has polycyclic disease course and some continue to have active disease for years and well into adulthood, with significant impacts on quality of life.

**Summary**
These recent findings have considerable implication on clinical practice regarding diagnosis, treatment, and monitoring of the disease. Collectively, they support the need for continued monitoring of the disease and screening using comprehensive imaging, such as WBMRI.

**Keywords**
autoinflammatory bone disease, chronic nonbacterial osteomyelitis, chronic recurrent multifocal osteomyelitis in children, spine disease, vertebra plana

## INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disease that affects children and adolescents [1,2]. The average age at disease onset is 9–10 years with female predominance (2 : 1) [2]. The disease typically presents with bone pain with or without systemic features [2]. Association with other chronic inflammatory diseases, such as psoriasis and inflammatory bowel disease is well documented [2]. Innate immune activation and cytokine dysregulation play a major role in CRMO pathogenesis [2]. Furthermore, there is evidence of a genetic component to CRMO [2]. With lack of widely accepted validated criteria or diagnostic biomarkers, CRMO remains a diagnosis of exclusion [3▪]. Imaging including whole-body MRI (WBMRI) and sometimes bone biopsies are needed to support the diagnosis.

The nomenclature can be confusing with multiple names used for sterile osteomyelitis syndromes including chronic nonbacterial osteomyelitis (CNO), synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome, diffuse sclerosing osteomyelitis of mandible, and nonbacterial osteomyelitis (NBO) among many others used in the literature [1,4]. In this review, we will use the term CRMO.

The majority of literature reports good prognosis and favorable long-term outcomes in patients with CRMO. However, recent publications describe

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## KEY POINTS

- Disease activity in CRMO patients follows a polycyclic, waxing and waning course in the majority of patients.
- CRMO activity can persist for years with at least one quarter of patients demonstrating high rates of residual bone deformities, leg-length discrepancies, and pathological fractures.
- Involvement of vertebrae is common in patients with CRMO; spinal involvement can be present at onset and maybe asymptomatic. Vertebra plana can develop, particularly if untreated or inadequately treated.
- CRMO carries high disease burden affecting patient and their families. Patients frequently suffer from pain syndromes and psychosocial effects.
- Prospective cohorts are urgently needed for better subclassification of the disease, evaluation of risk factors for complications, and institution of effective therapy plans and long-term monitoring.

increased rates of complications and disabling sequalae in affected patients. In a subset of patients, there is ongoing inflammation for years. If untreated, persistent inflammation can result in bone destruction, severe continuing pain, growth disturbances, functional limitation, and pathological fractures [5].

Despite recent advances in understanding of the pathogenesis and radiological approach to CRMO, substantial questions regarding the risk of complication and approaches to therapy remain unanswered. In this review, we will focus on disease course, complications, and sequalae of CRMO in childhood. Recently published cohorts will be summarized and compared with earlier literature. We will highlight new findings and examine the potential for improvement in clinical care and disease monitoring.

## DISEASE COURSE

Although early literature suggested that the CRMO courses are typically benign and self-limited, more recent studies with larger cohorts and longer follow-up has suggested more variability. CRMO is characterized by unpredictable course that could include multiple relapses and flares in a waxing and waning fashion with the possibility of spontaneous remission. In children with CRMO, remission rate varied widely among cohorts ranging between 37 and 82.4% after 1–5 years of follow-up [6–13,14▪▪,15]. In one cohort with longer follow-up (average 12 years), remission was only achieved in about 40% [16]. Remission off medications was reported at lower rates ranging from 13 to 26% [6,9,11,17]. Median duration of active disease for those who achieved remission ranged between 3 and 5 years [17,18]. These studies used slightly different inclusion criteria, definitions of remission on and off medications, and wide range of follow-up duration. Cohorts with longer follow-up duration might have been subjected to selection bias by recruiting patients with rather unfavorable disease course. On the other hand, recent cohorts tended to use WBMRI more frequently detecting many asymptomatic active lesions. Most authors agreed that about a quarter of patients will have continued disease activity for years [11,18–20]. The duration of symptoms in this subset ranged between 7 and 25 years [18,21–23].

The majority of children with CRMO suffer from one or more recurrence during their disease course [8–10,12,15,18,20]. Disease recurrence and relapses were reported in 60 and 83% in two large cohorts [9,12]. In a recently published cohort from Ireland, 95% of patients followed a relapsing-remitting course [14▪▪]. Recurrence rates of as low as 20% have also been reported [10,20]. The higher rates of relapse in more recent studies may be attributed to better utilization of diagnostic modalities, such as WBMRI. In one study, MRI detected asymptomatic lesions in 47% of the patients [24]. The number of relapses ranged from 1 to 5, with a median time of 24 months between relapses [17,20]. In a study with average 12 years of follow-up, one-third of those with continued active disease followed a polycyclic pattern with flares occurring every 3–6 months. Two-thirds continued to have persistent course with daily symptoms [18].

The relationship of disease activity to the type and timing of treatment is not well studied, mostly because of lack of well phenotyped prospective cohorts. In one study 60% (17/28) of patients on nonsteroidal anti-inflammatory drugs (NSAIDs) monotherapy continued to have active disease [11]. In a recent study of 131 patients where almost 70% received bisphosphonates, only 32% were classified as recurrent disease at the time of follow-up [25].

In contrast to what was reported earlier, some patients with CRMO may have a poorer prognosis than previously described. There is more frequent active disease at follow-up, and at least 25% of patients will suffer continued disease activity years after diagnosis despite treatment. This highlights the importance of long-term follow-up and disease monitoring.

## CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS AND THE SPINE

Described as a rare event with few case reports early on [26–28], the association between vertebral plana and CRMO was first reported in a case series by Yu *et al.*, in 1989 [29]. In their series of seven children with disease at various sites, there were 11 lesions involving the spine including three cases of vertebra plana [29]. In 1998, Baulot *et al.* [30] described a case of CRMO with neurologic deficits caused by vertebra plana, thoracic kyphosis and spinal cord compression. Since that initial report, there have been many reports of spine involvement, sometimes complicated by vertebra plana in association with CRMO [27,31–36]. This demonstrates that while CRMO often involves the periphyseal regions of the lower extremities, it may present with isolated spine involvement [37,38].

Spine involvement is now considered a classic finding in CRMO (Figs. 1 and 2), its incidence varies significantly in different cohorts ranging from 2 to 10% in some studies [13,39▪▪,40–42] and as high as 35% in others [7,16]. This variability could be because of differences in radiologic strategies used to determine extent of disease as spine lesions can be asymptomatic and would be missed if only painful sites are imaged. In a recent cohort of 15 patients where WBMRI was used at diagnosis and for disease monitoring, 66.7% had vertebral lesions [15]. This underscores the importance of using whole body imaging, preferably WBMRI, at diagnosis and follow-up to avoid missing asymptomatic lesions, especially of the vertebrae.

In the majority of cohorts, about 25–30% had spinal lesions with CRMO, sometimes at disease onset [9,11,12,14▪▪,20,43–46]. The thoracic spine is the most commonly involved vertebral site in many case reports and cohorts [20,28,43–45,47]. Spinal lesions are usually multifocal and tend to involve noncontiguous vertebrae (Figs. 1 and 2) [28,44], and spares the disk [31,43] although contiguous vertebra can be involved [43,48].

In a retrospective cohort focusing on spine disease by Hospach *et al.*, 26% of all CRMO patients had spine disease. Most alarming was that in 25% of the cases, spine disease was asymptomatic and some had spine deformities [45]. Asymptomatic spine lesions were also reported by others [16,43,47]. This highlights the importance of screening for these lesions even in asymptomatic patients using dedicated spine visualization.

Skeletal deformities with fractures in the growing skeleton are prevalent in CRMO [7,18,22,29,31,35,45,46,49,50]. Kyphosis and scoliosis as consequences of CRMO are frequently reported [7,9,13,20,35,43,45], including drastic

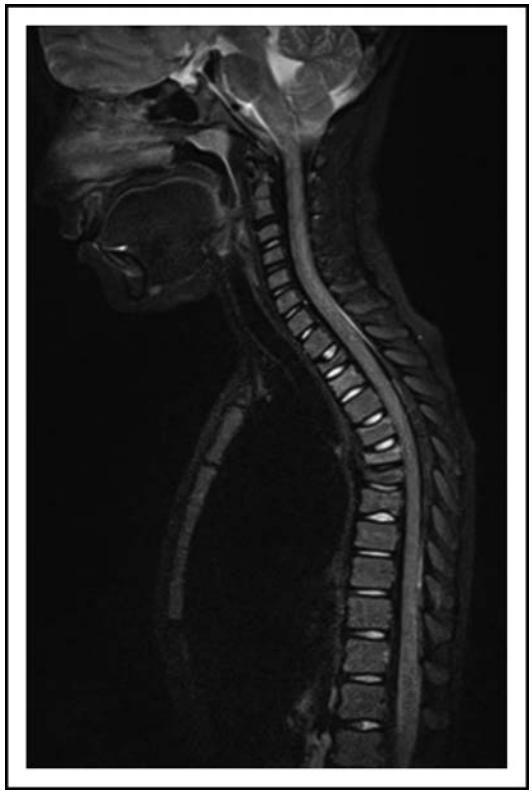

**FIGURE 1.** Spine disease in chronic recurrent multifocal osteomyelitis: 6-year-old boy with chronic recurrent multifocal osteomyelitis and multiple compression deformities.

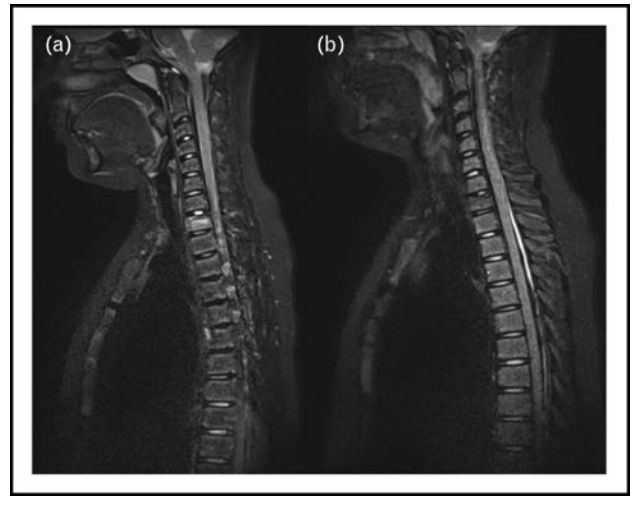


**FIGURE 2.** Spine disease progression in chronic recurrent multifocal osteomyelitis: 14-year-old girl with known chronic recurrent multifocal osteomyelitis. (a) MRI demonstrates increased STIR signal in the T1 vertebral body. (b) Follow-up 6 months later demonstrates resolution of marrow edema but interval development of mild superior endplate compression. STIR, Short Tau Inversion Recovery (MRI sequence).

presentation and acute onset scoliosis [36,49]. In a cohort of spine disease in CRMO, 22% had scoliosis or kyphosis requiring orthopedic corset [45], and almost 50% of patients with vertebral disease ended up with scoliosis in another cohort [7]. Prior reports document ~20 to 40% of those with vertebral lesions develop vertebral fractures or collapse [6,9,11,12,15]. Yet, in a recent cohort of 44 patients, 80% of those with vertebral lesions (10 total) developed compression fractures [14▪▪]. Most concerning is that for many patients, these complications were reported at the time of initial imaging [14▪▪].

To date, risk factors for spine disease in CRMO are unknown. One study reported that female sex, multifocal involvement, and absence of involvement of the foot bones are independent risk factors of spinal involvement [44]. In a large French cohort, the only observed difference between those with and without spine disease was the use of 'aggressive treatments' per the authors [6]. Another cohort observed that patients with vertebral compression fractures had delayed diagnosis [15]. There may be geographic variability in the incidence of spine involvement. In an international retrospective cohort, patients from Italy had significantly higher vertebral involvement (50%) when compared with patients from France, Slovenia, and India [24]. Although no conclusions can be made based on one study, exploration of genetic and epigenetic effects on vertebral involvement and its progression is warranted.

In light of recent reports of higher incidence of spine disease, presence of asymptomatic lesions, and advanced complications at onset, regular and active screening for vertebral involvement is prudent. Frequent screening with WBMRI is important for early detection, close monitoring, and effective therapy. Treatment regimens with bisphosphates might be superior in vertebral involvement, for its bone strengthening properties. There are reports of improvement of vertebral shape in a few patients treated with bisphosphonates [51]. There is no consensus on how often imaging should be performed to monitor disease activity in CRMO. In North America, about half of the surveyed pediatric rheumatologists use imaging 'regularly', with half of them repeating imaging every 6 months [52].

Some authors suggested that CRMO eventually evolves to a more classic axial spondyloarthropathy [53], yet others report no evolution of disease in the majority of the cohort [18,20]. One study reported evolution to spondylarthritis only in CRMO cases with continued inflammation [12]. It is interesting to note that in most reports, HLA-B27 positivity is not enriched in patients with CRMO [1].

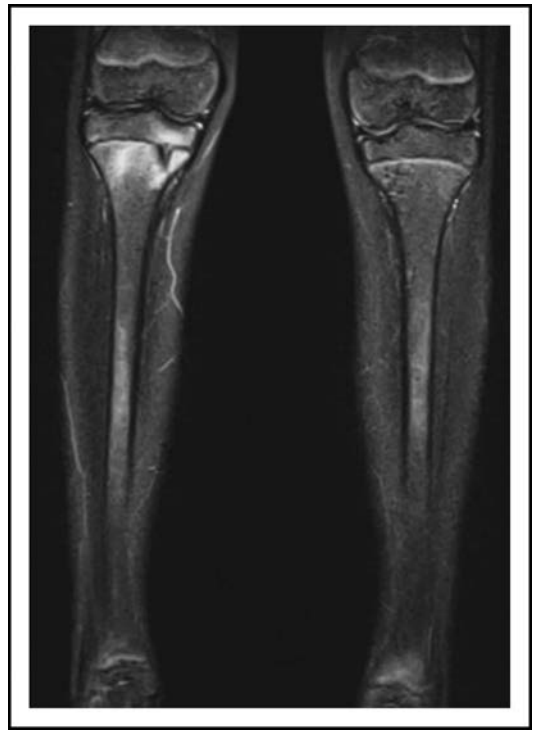

**FIGURE 3.** Ten-year-old girl with chronic recurrent multifocal osteomyelitis and a small physeal bar in the proximal right tibia.

## OTHER BONY COMPLICATIONS

Bony complication with CRMO were reported as early as 1987 by King *et al.* [34]. These include spontaneous fractures, leg-length discrepancies, physeal bars (Fig. 3), bone hyperostosis, and joint angulation [2]. It is suggested that pathologic fractures are attributed to accelerated bone resorption. Leg-length discrepancies may develop because of growth plate involvement and overgrowth of the epiphysis because of inflammation (Fig. 4). Damage to the growth plate can result in joint angulation [2]. Whenever CRMO affects the jaw, hyperostosis and persistent mandibular swelling often occurs [12].

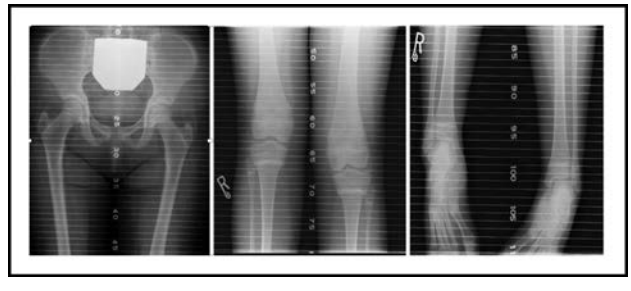

**FIGURE 4.** Leg-length discrepancy in chronic recurrent multifocal osteomyelitis. Images of 14-year-old girl with left leg 2 cm longer than right, secondary to hyperostosis of left femur.

In large cohorts, 20–26% developed sequalae and bone deformations with CRMO [6,19]. In two long-term follow-up studies, about 50% suffered bone deformities [18,22] with 30–40% developed leg-length discrepancies [18,22]. Long-term cohorts might be biased by response rate, as subjects with more persistent disease and sequalae are more likely to participate in these studies whereas those doing well may not return for follow-up.

Pathological fractures were reported in 29% in one study [7]. Fractures were reported mostly not only in the vertebrae but also in the acetabulum, clavicle, cuboid, femur, tibia, and metatarsus [7,10].

## NEUROLOGICAL AND VASCULAR COMPLICATIONS

Although extremely rare, multiple case reports and series reported nerve and vessel compressions as a result of CRMO. Complications secondary to persistent hyperostosis of the clavicle have been described including neurovascular compression, such as thoracic outlet syndrome [12,18,47,54]. Multiple cases of occipital, facial, and orbital bone involvement were reported resulting in recurrent headaches, periorbital swelling, and facial palsy [55–59].

## IMPACT ON QUALITY OF LIFE

CRMO has huge impact on the quality of life and psyche of affected children and their families. Impacts secondary to fatigue and pain are significant. Effects on daily activity, school and work, and psychosocial well being were observed in multiple studies. Silier and colleagues highlight the difficulties of CRMO from the patient perspective. In their cohort of 105 patients, about 80% reported CRMO had a negative influence on their family, friends, and work [60]. Psychosocial complications were more frequent than physical complications in one cohort of 44 patients, with about one-third affected [14▪▪]. In a study of 284 patients by Oliver *et al.* [5], more than half of patients reported that CRMO negatively affected their participation in activities, school or work attendance, and school performance. These effects were largely attributed to fatigue, pain, and physical limitations because of CRMO [5]. Effects extended to parent's job attendance, performance, and family finances [5]. Negative effects on psychosocial well being with depression, anxiety, anger management, and personal relationships were reported in one-third of patients [5]. Similar effects on education, sports participation, job performance, psychological disturbance, adverse effects on quality of life, and global repercussion on life were reported by others [17–19,61].

Increasingly, physicians are noting that many CRMO patients develop amplified musculoskeletal pain but there is limited published data on its incidence in CRMO patients. In a recent study, CRMO was complicated by pain amplification syndrome in 10 of 44 patients [14▪▪], similar rates were also reported by others [18]. It is interesting to note that lower rates were reported previously [6,10]. The higher rates in recent studies might reflect use of WBMRI that allowed better identification of active disease based on imaging findings instead of clinical symptoms only, particularly in those who present with diffuse pain amplification as a prominent symptom as the diagnosis can be missed without imaging.

More studies are needed to address the impact of CRMO on patients and their families; these can be used to better tailor guidance and support. Need for school accommodations and psychosocial support should be considered and implemented early in the disease course to improve the quality of life for these children and their families. In one study, only 36% of patients had formal school accommodations in place, such as 504 plans [5]; whereas in another, 75% of all patients received no psychosocial guidance [60].

## CHILDHOOD CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS INTO ADULTHOOD

Although the prognosis of patients with CRMO is generally believed to be good, at least a quarter of patients have continued disease activity or residual sequalae into adulthood. Yet, only few studies assessed the long-term effect on adults with childhood CRMO. In a study by Duffy *et al.* [22], with a mean of 14 years of follow-up after onset of childhood CRMO, 60% had visible deformities and some walked with an obvious limp. Another study with a mean 15 years of follow-up reported active lesions into adulthood in more than 50% [16]. Selection bias might have affected the results of these studies as not all of the participants from original cohorts responded to follow-up questionnaires. Further research is needed to determine disease burden in young adults with childhood onset CRMO.

## CONCLUSION

With the increasing use of WBMRI in recent studies, more disease activity and complications are being reported. This suggests that long-term outcomes in patients with CRMO may not be as favorable as previously suggested. The disease can have a heavy burden on patients and their families with ongoing disease activity and sequalae in at least

25% of patients. It is clear that CRMO is a disease with variable severity. It can be monofocal with self-limited course, or can be multifocal and persistent. Many have no long-term sequelae, yet others are left with bone deformities and suffer from chronic pain. Early diagnosis, prompt control of inflammation, and continued monitoring is warranted to avoid complications and sequalae. Further research is needed, particularly in regard to identifying those who are at risk of long-term disease-associated sequelae.

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## Conflicts of interest

*There are no conflicts of interest.*

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# Health inequities in the rheumatic diseases of childhood

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**Purpose of review**
To describe differences in disease manifestations and outcomes in pediatric rheumatic diseases as they occur in non-European-descended populations in North America.

**Recent findings**
Differences in disease prevalence, clinical phenotypes, disease course, and outcomes have been described across the spectrum of pediatric-onset rheumatic diseases. Although these differences are commonly explained by differences in genetic risk or access to tertiary healthcare facilities, our emerging understanding of the immunobiology of historical/ongoing trauma suggest a more complex explanation for these observed differences.

**Summary**
Health inequities as observed in pediatric rheumatic diseases are likely to emerge from a complex interplay between social and biological factors. The important contribution of historical and repetitive trauma deserves further exploration.

**Keywords**
adverse childhood experiences, health inequities, pediatric rheumatic disease

## INTRODUCTION

The purpose of this review is to outline differences in pediatric rheumatic disease prevalence and outcome among different ethnic groups and ancestries when compared to European-descended populations in North America. After discussing the prevalence and outcomes, we will explore the factors that may account for these differences. These include the social factors, such as limited access to healthcare and adverse childhood experiences.

Note: It is well understood that the concept of 'race' is a purely social construct having no objective validity in biology. Indeed, while the concept of race is often misused in medicine as a proxy for ancestry [1▪▪], the two terms are not equivalent. Although many of the articles we cite here use race as if it were an objective term, we have, wherever possible, preferred to use the term *ancestry* whenever referring to certain socially identifiable groups.

## JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the most common childhood-onset rheumatic disease [2]. There is, however, relatively little data on this disease entity in non-European populations in North America. Most studies report disease rates at least as high as those identified in children of European ancestry [2–6], as well as subtype-specific differences.

Subtype-specific differences have been noted in the African American population. For example, this group has an increased prevalence of rheumatoid factor (RF)-positive polyarticular JIA compared with the non-Hispanic European (NHE) population [3,4], where this subtype is relatively rare. African American children also have an older age of onset, even after adjusting for the higher rates of RF-positive disease [3]. In contrast, the NHE population is more likely to have ANA-positive oligoarticular JIA, a subtype that carries a high risk for developing chronic uveitis [3,4,7]. This observation is consistent with the previous report that the prevalence of

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## KEY POINTS

- Differences in prevalence, phenotype, clinical course, and outcome have been observed in pediatric rheumatic diseases when European and non-European-descended populations are compared.
- Although these differences are often attributed to genetic influences, emerging data on the immunobiology of historical and repetitive trauma suggest a more complex cause for observed disease differences.
- Links between adverse childhood experiences and pediatric rheumatic diseases need to be explored further.

uveitis is lower in the African American population than in NHE [4]. However, a more recent study by Fitzpatrick *et al.* [3] reported that the rates of uveitis did not differ significantly between African American and NHE populations. Both the Schwarz and Fitzpatrick studies report a higher percentage of African American children with systemic-onset JIA than in the NHE [3,4].

Studies have also been done to characterize the phenotype of JIA in the indigenous populations of Canada, Alaska, and the lower 48 states of the United States. Generally, the findings in the indigenous populations are similar to those reported in African American populations. For example, in a study of two Indian Service user populations, Mauldin *et al.* [6] estimated that the prevalence rates of JIA were at least double those estimated for European populations. The distribution of the age of onset observed in the Indian Health Service user populations also differed from that reported in children of European ancestry. In NHE, there is a distinct peak of new cases in the later preschool years, likely reflecting the frequency of oligoarticular-onset disease in this age group. In the American Indian populations, this peak was not observed, consistent with the observed rarity of early-onset oligoarticular disease in the Indian Health Service user population.

This is not to say that oligoarticular disease does not occur in the indigenous population. Although the Mauldin study [6] found that oligoarticular onset disease was rare in indigenous preschoolers, Khondra *et al.* [2] found that oligoarticular JIA is the most common form of JIA in the Alaskan Native population. These findings may reflect a population of older children with oligoarticular onset disease, as the median age of onset for all JIA was 9.1 years for the Alaskan population [2], slightly older than the 6.1 years reported in a recent study for NHE [3]. There is an increased prevalence of RF-positive polyarticular JIA in Canadian Native population [5] as has been reported in the African American population [4].

In addition to differences in phenotype or the differences in the distribution of the common JIA sub-phenotypes, a small number of studies has recently been directed toward determining whether outcome for JIA differs according to race/ethnicity/ancestry. These studies have to be interpreted with the understanding that children of both African and indigenous ancestry are more likely than children of NHE ancestry to be RF-positive, a factor that already places them at higher risk for more severe disease and poorer functional outcomes [7,8].

Several studies have noted differences in outcomes associated with JIA in the different populations. Analyzing the Childhood Arthritis and Rheumatology Research Alliance Registry (CARRA), Ringold *et al.* [9] showed that African American children have more disease activity and joint damage compared with European descended children. The study also found a significant difference in the number of African American children who received treatment with biologic agents compared with European descended children. The authors attributed increased frequency of biological treatment to African American children's having increased severity of disease and is consistent with the higher frequency of RF-positive disease in these groups. Whenever considering polyarticular JIA only, African American children have higher levels of joint damage compared with the European descended children [9], once again a feature of the disease for which RF-positive children are at higher risk.

There also appear to be differences in how JIA is experienced with children of NHE ancestry are compared to children of non-European ancestry. For example, in the Ringold study, the median pain scores reported by African Americans was 3.1 out of 10 compared with 2.6 for NHE children, suggesting a difference in pain experienced by the participants. In the Hispanic population, there were reports of increased pain and joint damage, although, after adjusting for multiple factors, such as demographic characteristics, social economic status, and disease characteristics, these results were no longer significant. This finding illustrates the complexity of isolating a single variable in considering disease course and outcome, where multiple intersecting factors are likely at play [9].

The findings from the Ringold study [9] were corroborated more recently by Chang *et al.* [10]. This study compared JIA outcomes based on a treat-to-target strategy and found that, at the initial visit African American children had higher pain scores

and lower mobility compared with the NHE children [10]. The authors also noted that there was no significant difference in improvement between the different groups of children: most of the children improved throughout the study. However, throughout the duration of the study, African American children 'had persistently greater disease activity' and 'greater joint damage' compared with the European children [10]. Thus, in both the Ringold and Chang studies, African American children had worse disease course (in terms of persistent disease activity), pain, and damage. Although these data are provocative, it remains unknown whether these findings can be explained exclusively on the higher rates of RF-positive disease in African-descended populations. A study comparing subtype-matched patients (e.g. focusing specifically on outcomes for RF-positive disease) among different ethnic/ancestral groups will be needed to clarify this issue.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by brisk autoantibody expression and subacute/chronic inflammation involving multiple organ systems. The literature discussing pediatric-onset SLE in different ethnic/ancestral groups is sparse, and thus, possible effects/outcomes associated with ethnicity/ancestry must be described from the adult literature [11–13]. In the adult population, studies suggest higher rates of SLE in African America, Hispanic, Asian, and Native American populations compared with NHE populations [11–13]. To a limited extent, the higher rates can be corroborated in the pediatric populations. For example, a study of the prevalence of pediatric SLE in the Native population in British Columbia, Canada found that SLE prevalence rates were 2.5 times higher than for non-Natives [14]. Another study from Toronto noted high rates of SLE in in pediatric populations with non-European ancestry [15].

As seen in JIA, there are differences in disease presentation among different ethnic and ancestral groups. In a study conducted at Sick Children's Hospital in Toronto, the authors found children with SLE of non-European ancestry were diagnosed at a younger age compared with children of European ancestry. Children with African ancestry were diagnosed at the youngest age [15]. Children of European ancestry more likely to have malar rash and photosensitivity. Renal disease and discoid rash were more common in children with non-European ancestry. Interestingly, this finding differs from the Alaskan and American Indian adult populations where discoid rash was not a common finding [13].

Whenever compared with adult-onset disease, childhood-onset SLE is known to be associated with poor disease outcome [16]. Compared with adult-onset SLE, adolescent-onset displays more active disease, renal involvement, CNS involvement, hospitalizations, and increased morality [16]. As children of non-European ancestry are diagnosed at an early age and more likely to have renal manifestations, these populations may be especially vulnerable to poorer long-term outcomes.

## DERMATOMYOSITIS

Juvenile dermatomyositis is a disease characterized by muscle weakness and rash. The literature illustrating the ancestral differences in incidence and prevalence rates in the pediatric population is limited. However, a national study conducted in 1995–1998 estimated incidence rates of dermatomyositis in the pediatric population. The annual incidence rates were 3.4 per million children for NHE, 3.3 million African American non-Hispanic, and 2.7 million Hispanic children. In all three populations, there was higher female-to-male ratio [17].

Despite relatively similar incidence rates, the disease outcome is not the same when one examines children from different ethnic groups. For example, children of African descent have higher rates of calcinosis and worse disease activity [18]. The higher rates of calcinosis in African American children (compared with European-descended children) are concerning, given that calcinosis results from chronic, smoldering disease and is associated with delayed diagnosis and treatment [19]. Whether delayed diagnosis might be because of limited access to the healthcare system, epigenetically mediated biological differences, or other factors is unclear. Delayed diagnosis may also emerge because of lack of familiarity by treating physicians with the appearance of the disease-defining rash as it appears in patients with darker colored skin. Finally, it is urgent that the field also explore the possibility that the chronic, smoldering disease in African American children is a reflection of unconscious bias or differences in treatment approach among providers.

## THE CHALLENGE OF LACK OF DATA

It is important to point out that the current literature on rheumatic diseases in children lacks sizable populations of minority groups. In the treat-to-target intervention paper [10], for example, there were 159 total pediatric patients included in the study. Among these, 117 children identified as Caucasian, 21 children identified as African American, and 21 identified as Asian/Other. Similarly, another study

[18] reported a total of 438 subjects, with 347 of whom were identified as being 'Caucasian,' with 57 (13% of the total) identified as African American, and 34 patients identified as 'minority, nonblack'. In general, published studies under-represent minority groups as they are reflected in the population of the United States. There is some reason to be hopeful that the Children's Arthritis & Rheumatology Research Alliance patient registries will gradually capture this broader population. The current registries have data from more than 10 000 children, 30% of whom are identified as 'nonwhite' (Dr Colleen Correll, personal communication). At the same time, only 5% of the patients in the registries are identified as African American.

## UNDERSTANDING HEALTH INEQUITIES THROUGH A HISTORICAL–BIOLOGICAL PERSPECTIVE

When one identifies differences in disease prevalence or outcome in a distinct, socially identifiable group, it may be tempting to attribute these observations solely to genetic influences [20–23]. Although there is no question that there are genetic risks for complex traits that are specific to specific ancestral groups [24,25], genetic susceptibility alone does not provide a satisfactory explanation. First, relying entirely on 'genetic explanations' should give us pause, as implicit in this interpretation is the idea, resented by vulnerable populations that the affected groups are more likely to be ill as they have 'bad genes'. Although genetic explanations are not implicitly racist, they facilitate the idea of 'otherness' between the European-descended 'comparison group' and the population of interest.

Similarly, it is easy for physicians to reach the conclusion that inequities in health outcome largely reflect lack of access to care [26].

There is little doubt that multiple factors, from geography, to poverty, to the precarious status of the publicly funded heath delivery system (in the United States, at least) both limit access and affect outcomes. However, it should be acknowledged that over-emphasizing access as a driver of health inequities can be both self-serving, as it is accompanied by the underlying assumption that the primary drivers of health inequities are medical and addressable with medical solutions. This ignores important new discoveries about the basic biology of social marginalization and historic/repetitive trauma [27].

The Adverse Childhood Experiences (ACE) study [28], is perhaps the most important public health study to emerge since the Framingham Study. Although the latter linked multiple environmental and behavioral factors to cardiovascular disease [29], the scope of the former is broader and of potentially higher impact. The ACE study, undertaken with a population enrolled in the Kaiser Permanente health system in California, identified strong links between specific traumatic events in childhood and adult health outcomes. Initially, these findings were view through the lens of disrupted neuropsychological development [30,31], which, this interpretation suggested, led to risky health behaviors (e.g. smoking, alcohol and drug abuse), and thus, an increased burden of chronic diseases. However, our emerging understanding of the biology of historical and repetitive trauma [32▪▪,33] makes it clear that the types of trauma experienced by socially marginalized and vulnerable populations may have biological effects that extend beyond the central nervous system. These include well documented effects on the immune system [34▪▪,35], which may be drivers of autoimmunity.

This leads us to the 'elephant in the living room:' *why* is it that populations that have the highest prevalence rates of rheumatic disease (e.g. indigenous Americans, who have the higher rates of both rheumatoid arthritis [36] and systemic lupus [13] than the broader population) should also be populations that have experienced significant historical trauma and still face the challenges of racism and social/economic marginalization? Is it a coincidence that ACE scores are also higher in these populations [37]? At the present time, the field has yet to unequivocally link the incidence or prevalence of rheumatic disease to ACEs per se [38], although there's tantalizing evidence to make this link [39,40▪]. There is accumulating data that the higher ACE scores affect clinical course and outcome [41,42], and thus, the observed differences in outcomes that we have reviewed in the article need to be considered in the light of what we now know about the impact of early childhood experiences.

## CONCLUSION

There are discernable differences in disease prevalence, clinical manifestations, and outcomes when children from different ethnic/ancestral backgrounds are compared with children of European ancestry. These differences may reflect small differences in risk conveyed by ancestry-specific genetic haplotypes and/or social factors, such as access to healthcare. However, our evolving understanding of the biology of historical and ongoing stress/trauma invites new ways to interpret these findings.

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## Conflicts of interest

*There are no conflicts of interest.*

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# Complications of severe acute respiratory syndrome coronavirus 2 infection in children

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**Purpose of review**
Although during the initial stages of COVID-19 pandemic, the pediatric population seemed to be less affected, a number of SARS-CoV-2-related manifestations emerged over time, the principal of which is the multisystem inflammatory syndrome in children (MIS-C). Here we provide an update on the main pediatric disorders associated with SARS-CoV-2 infection.

**Recent findings**
MIS-C is novel postinfectious manifestation with clinical features similar to Kawasaki disease and characterized by intense systemic inflammation affecting multiple organs. Many children required intensive care therapy because of circulatory shock, usually of myocardial origin. Appropriate treatment with immunomodulatory therapies led to favorable outcomes in most patients, with recovery of overall health and cardiac dysfunction. In addition to MIS-C, a variety of other complications of COVID-19 in children have been described, including thrombotic events, neurologic manifestations, and chilblain-like lesions. There is still uncertainty about the true prevalence of long COVID in children and its distinction from pandemic-related complaints.

**Summary**
The experience gained so far with MIS-C and the other SARS-CoV-2-related complications in children and adolescents will facilitate accurate diagnosis and appropriate treatment. Further studies are needed to elucidate the pathophysiology of MIS-C and to determine the real impact of long-COVID in the pediatric age group.

**Keywords**
coronavirus disease 2019, hyperinflammation, Kawasaki disease, multisystem inflammatory syndrome in children, severe acute respiratory syndrome coronavirus 2

## INTRODUCTION

In November 2019, a novel coronavirus was identified in Wuhan, China, as the cause of a cluster of severe cases of pneumonia and acute respiratory distress syndrome [1]. The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was termed coronavirus disease 2019 (COVID-19). The infection rapidly spread throughout the world, leading the WHO to declare a pandemic on 11 March 2020. Thus far, reported cases of COVID-19 in the United States have exceeded 80 million and have resulted in nearly one million deaths [2].

Initial data indicated that most children who contracted SARS-CoV-2 were asymptomatic or mildly symptomatic and that only a few needed hospitalization and admission to the ICU was rare [3]. This scenario changed in April 2020 with the reports from the UK and Italy of children presenting with fever and hyperinflammation temporarily associated with COVID-19 and with clinical features similar to those of Kawasaki disease, toxic shock syndrome (TSS), macrophage activation syndrome, or bacterial sepsis [4,5]. This condition was named multisystem inflammatory syndrome in children (MIS-C) by the US Centers for Disease Control and Prevention. However, a number of other clinical manifestations of COVID-19 in

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## KEY POINTS

- A wide spectrum of SARS-CoV-2-related clinical manifestations has been described in children and adolescents.
- The multisystem inflammatory syndrome in children (MIS-C) represents the most serious and challenging complication of SARS-CoV-2 infection in the pediatric population.
- Appropriate immunomodulatory treatment of MIS-C has led to favorable outcomes in terms of recovery of overall health and cardiac dysfunction.
- The other main complications of SARS-CoV-2 infection include thrombotic events, neurologic manifestations, and chilblain-like lesions.
- The real prevalence and impact of long COVID symptoms in children is still uncertain.

children have emerged over the course of the pandemic (Table 1).

The objective of this review is to describe the recently published data on MIS-C and the other main complications of SARS-CoV-2 infection in children.

## MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

The emergence of MIS-C has represented one of the most worrying and mysterious phenomena observed during the COVID-19 pandemic. The signs and symptoms of this hyperinflammatory condition are a mix of those of Kawasaki disease (Figs. 1 and 2) and TSS, and are characterized, among others, by fever, gastrointestinal symptoms (nausea, vomiting and abdominal pain), and cardiac involvement, especially myocarditis. Many of these children have required urgent ICU admission because of the development of multiorgan failure and circulatory shock, usually of myocardial origin. Laboratory abnormalities include markedly increased acute phase reactants, raised ferritin and D-dimer, hypoalbuminemia, lymphopenia and relative thrombocytopenia. Patients with myocarditis have elevated levels of pro-B-type natriuretic peptide (proBNP) and/or troponin. After the initial reports, the frequency of MIS-C has increased sharply in many areas of the world. Case definitions and diagnostic criteria have been published by several central agencies to facilitate its recognition.

Over the last year and half, there has been an increasing number of reports of MIS-C and much has been learned about this condition [6▪▪–8▪▪,9▪,10▪]. In the largest study of 1733 patients, its incidence has been estimated to be 2.1 cases per 100 000 children [8▪▪]. The incidence per 1 000 000 SARS-CoV-2 infections was 316 persons. The median age of affected patients is 7–8.9 years and there is a slight male predominance [7▪▪]. In United States cohorts, black and Hispanic children were overrepresented [7▪▪,11▪]. Patients younger than 4 years had the lowest frequency of severe manifestations, whereas those aged 18–20 years had the highest proportions of myocarditis. Among the 1733 patients described by Belay *et al.* [8▪▪], the mortality rate was 1.4%. Epidemiologic data indicated that the onset of MIS-C occurred 2–5 weeks after prior

**Table 1.** Complications of severe acute respiratory syndrome coronavirus 2 infection in children

| | |
|---|---|
| Systemic | Multisystem inflammatory syndrome (MIS-C) |
| | Macrophage activation syndrome |
| | Coagulopathy |
| | Vasculitis |
| | Sepsis |
| | Cold abscesses |
| | Long COVID |
| Cardiovascular | Thromboembolism |
| | Myocarditis |
| | Pericarditis |
| | Acute heart failure |
| | Arrhythmia |
| | Coronary artery dilatation or aneurysms |
| Neurological | Seizure |
| | Meningitis/encephalitis/encephalopathy |
| | Acute disseminated encephalomyelitis (ADEM) |
| | Myelopathy |
| | Acute ischemic and haemorrhagic stroke |
| | Neuropathy |
| | Guillain–Barre' syndrome |
| | Chorea |
| | Psychosis |
| Renal | Acute kidney injury |
| | Glomerulonephritis |
| Respiratory | Pneumonia |
| | Acute respiratory distress syndrome |
| Ophthalmic | Conjunctivitis |
| | Optic neuritis |
| | Uveitis |
| Dermatological | Chilblain-like lesions |
| | Erythema multiforme |
| Gastrointestinal | Mesenteritis |
| | Appendicitis |
| | Pancreatitis<br>Hepatitis |
| Endocrine | Diabetic ketoacidosis |

**FIGURE 1.** Conjunctival injection sparing the limbus in a child with multisystem inflammatory syndrome.

infection or known exposure to SARS-CoV-2, suggesting a postinfectious phenomenon [6▪▪].

On the basis of similarities with Kawasaki disease, intravenous immunoglobulin (IVIG) at 2 g/kg dosing is considered the mainstay of initial treatment of all cases of MIS-C. However, recent studies have shown that early administration of glucocorticoids, with or without IVIG, is associated with a lower risk of cardiovascular complications and need for adjunctive therapy as compared with IVIG alone [12]. Moreover, IVIG with methylprednisolone has led to lower rates of treatment failure, less hemodynamic support requirement and decreased length of ICU stay than did IVIG alone [13]. A retrospective cohort study has shown that glucocorticoid monotherapy can be a suitable therapeutic option for MIS-C patients with mild disease [14]. In some instances, particularly after inadequate response to IVIG and glucocorticoids or in case of severe myocarditis with myocardial failure, IL-1, IL-6 or tumor necrosis factor inhibitors are given. With an approach based on a multistep anti-inflammatory treatment protocol, based on disease severity at admission, no patient required admission to ICU, invasive mechanical ventilation, or inotropic drug administration [15▪]. For more detailed information about the management of MIS-C, the readers are referred to the recommendations published by scientific societies or networks [16▪▪,17].

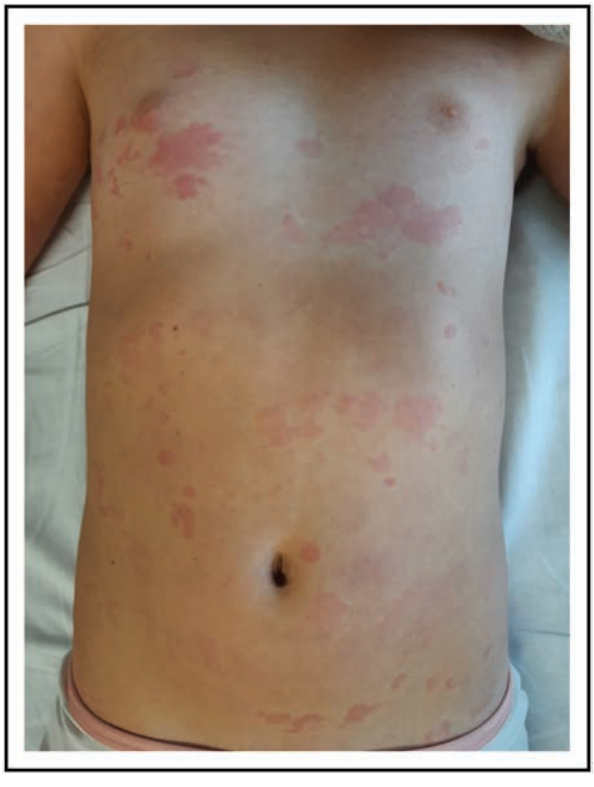

**FIGURE 2.** Erythematous rash over the trunk in a girl with multisystem inflammatory syndrome.

Overall, the vast majority of MIS-C patients do well with appropriate therapy and recover from their illness, regardless of severity. Although cardiac function abnormalities in patients with myocardial failure have been shown to recover in parallel with resolution of systemic inflammation, concern remains about the risk of long-term cardiac sequelae. Reassuring data were provided by Matsubara *et al.* [18▪], who found that cardiac outcomes of 60 MIS-C patients (70% of whom with myocardial injury) 3–4 months after initial presentation were good, with resolution of coronary aneurisms, no persistent clinical dysfunction on echocardiography and absence of fibrosis on cardiac MRI.

The clinical similarities between MIS-C and Kawasaki disease have stimulated an intense debate about whether MIS-C and Kawasaki disease represent different illnesses with overlapping clinical features or are on the same disease spectrum. Most experts favor the assumption that MIS-C is distinct from Kawasaki disease, based on epidemiological, clinical and immunological differences between the two entities [19,20▪,21▪]. Others, including the authors of this article, have argued that the two disorders may be a continuum, with some of the differences in phenotypic severity being because of the magnitude or kinetics of the immune response [22,23▪▪]. Particular genetic determinants may also play a role as rare inborn errors of immunity altering the immune response to SARS-CoV-2 have been highlighted as possible pathogenetic factors of MIS-C in some children [24▪▪]. An artificial intelligence-guided signature revealed a host immune response shared between MIS-C and Kawasaki disease [25].

## THROMBOTIC COMPLICATIONS

A significant prevalence of thrombotic complications has been described in adults with COVID-19. This risk has been attributed to the presence of a hypercoagulable state, which has led to the publication of guidelines on anticoagulant treatment in patients with COVID-19 [26]. Although some indications for anticoagulant prophylaxis that take into account individual risk factors, have been proposed [27,28], the risk for thrombosis in children with COVID-19 remains uncertain.

A few studies have investigated the prevalence of thrombotic complications in children with SARS-CoV-2 infection. A multicenter national Spanish cohort showed that only 4 (0.7%) of 537 infected children experienced a thrombotic event [29]. Three of them were adolescent girls, and only two had thrombotic risk factors. One patient was receiving thromboprophylaxis with heparin before thrombosis. None was diagnosed as MIS-C. Elevated D-dimer value did not predict vascular thrombosis.

In a multicenter retrospective cohort study of 853 children hospitalized for SARS-CoV-2-related complications, 20 instances of thrombosis were observed, including one stroke [30▪]. Patients with MIS-C had the highest incidence (6.5%). More than two-third of thromboses occurred in patients receiving thromboprophylaxis. Age at least 12 years, cancer, presence of central venous catheter, and MIS-C were significantly associated with thrombosis on multivariable analysis. Mortality rate was much higher in patients with thrombotic events than in the overall cohort (28 versus 2.3%), although most patients with fatal outcome had coexistent comorbidities that contributed to both thrombotic events and mortality.

A survey of international pediatric stroke subspecialists did not reveal an increase in pediatric ischemic strokes in the first 3 months of COVID-19 pandemic compared with the preceding 2 months [31].

Overall, current data indicate that thrombotic or thromboembolic events are uncommon in children with COVID-19, although the risk may be higher in MIS-C [32▪▪]. Notably, the proposed role of markedly elevated D-dimer levels in indicating the need for anticoagulant prophylaxis has not been confirmed. As a result, there is still little evidence to guide treatment decisions about anticoagulation therapy in children with SARS-CoV-2-related illness. Thus, the approach to coagulation management should be tailored to patient's individual risk factors [16▪▪].

## NEUROLOGIC COMPLICATIONS

Neurologic symptoms in patients with COVID-19 has been attributed to the interaction of SARS-CoV-2 with ACE2 receptors located in the central nervous system, cytokine-driven hyperinflammation, a hypercoagulable state or a molecular mimicry between viral and neurologic antigens [33▪▪,34▪]. The virus has been identified in CSF samples [35]. A broad spectrum of neurological manifestations has been reported in children, including loss of smell and taste, headache, stroke, dizziness, encephalopathy, acute myelitis, seizures, cranial neuropathy and cerebellar ataxia [33▪▪,36▪].

A systematic literature review identified 159 pediatric patients, aged from 24 h to 17 years, with severe neurologic manifestations [33▪▪]. Thirty-eight had cerebrovascular disease (ischemic and hemorrhagic strokes, venous thrombosis and cerebral arteriopathy), 32 various types of encephalitis (including acute disseminated encephalomyelitis, ADEM, anti-*N*-methyl-D-aspartate receptor, NMDAR, encephalitis), and 10 Guillain–Barré syndrome. In 65 patients, neurologic involvement occurred in the context of MIS-C.

A multicenter, cross-sectional survey investigated the prevalence and risk factors of neurologic manifestations in hospitalized children diagnosed with acute SARS-CoV-2 infection or MIS-C [36▪]. Overall, 44% of the cohort (40% acute SARS-CoV-2 and 66% MIS-C) had one or more neurologic symptom. The most frequent in the two groups were headache (16 and 47%, respectively) and acute encephalopathy (15 and 22%, respectively). Different patterns of neurologic manifestations were seen in children with SARS-CoV-2 or MIS-C.

A prospective national cohort study in the UK identified 52 pediatric cases of neurological and psychiatric complications associated with SARS-CoV-2 infection [34▪]. An estimated prevalence of 3.8 cases per 100 pediatric patients was established in England. Fifty-two percent of the patients were classified in the COVID-19 neurology group and 48% in the MIS-C group. Diagnoses in the former group included status epilepticus, encephalitis, Guillain–Barré syndrome, acute demyelinating syndrome, chorea, psychosis, isolated encephalopathy and transient ischemic attack. Patients with MIS-C had more heterogeneous features, which constituted encephalopathy, peripheral nervous system abnormalities, behavioral change and hallucinations at onset.

## CHILBLAIN-LIKE LESIONS

A wide range of cutaneous manifestations have been described in association with SARS-CoV-2 infection

[37,38]. From March 2020, a growing number of reports of acral lesions resembling chilblains in young patients appeared in the literature [39,40▪]. Chilblain-like manifestations observed during COVID-19 pandemic (commonly referred to as COVID toes) differ from classic chilblains (pernio) by equal sex distribution, absence of triggering factors and involvement of the feet and occasionally the distal third of the legs [40▪].

Lesions occur most commonly in young, previously healthy patients, are rarely seen in children younger than 10 years and involve most frequently the feet. They are usually multiple, round, vary from a few millimeters to centimeters in size, and involve the entire toe with a clear demarcation at the metatarsophalangeal level. The overlying skin may appear erythematous, violaceous or purpuric and sometimes infiltrated. The periungual and subungual skin is also affected. Over time, the lesions may become vesciculo-bollous or evolve into dark-purple or black crusts.

Videocapillaroscopy studies have shown capillary changes, with dilatation, pericapillary edema and microhemorrhages [41▪]. These alterations appear more severe than those described in idiopathic chilblains (which does not exhibit microhemorrhages), suggesting a component of a systemic process. Unlike adult cases, in which around half of patients experience COVID-19 symptoms, though usually mild, children or adolescents are generally asymptomatic, although local pain and itching may occur. The course is self-limited with spontaneous regression without any treatment within 2–8 weeks from onset. Relief of local pain or pruritus may require the administration of oral analgesic or antihistamines. Use of topical or oral corticosteroids is controversial [42].

Most individuals with chilblain-like lesions have negative tests for SARS-CoV-2. This observation has led to hypothesize a late manifestation of the infection, when viral RNA is no longer detectable [43]. The relationship with SARS-CoV-2 has been substantiated by the observation of the recurrence of chilblains in parallel with subsequent waves of COVID-19 [44].

## LONG CORONAVIRUS DISEASE

In parallel with the increase in the incidence of SARS-CoV-2 infection, concern has been raised about continuing symptoms after the acute infection, such as insomnia, fatigue, headaches, concentration difficulties, muscle and joint pain and shortness of breath lasting for several months. This condition is known as 'long COVID' and has been defined by the WHO as persistent or fluctuating symptoms with an impact on everyday functioning following SARS-CoV-2 infection for at least 2 months that cannot be explained by an alternative diagnosis [45]. In contrast with the increasing number of reports of long COVID in adults, only few studies have investigated the long-term recovery from COVID-19 in children. In addition, earlier analyses are limited by inclusion of small cohorts, lack of control groups and nonstandardized assessment of symptoms [46▪▪,47▪].

Borch *et al.* [48▪] investigated long COVID symptoms and duration through an electronic questionnaire in a nationwide cohort study of 15 041 SARS-CoV-2 positive children and a control group of 15 080 children. Only 0.8% of SARS-CoV-2-positive children reported symptoms lasting greater than 4 weeks, when compared with the control group, suggesting that the true prevalence of long COVID is much lower than the 12–51% reported in previous studies. The most common long COVID symptoms were fatigue, loss of smell and loss of taste, dizziness, muscle weakness, chest pain and respiratory problems. Symptoms, such as concentration difficulties, headache, muscle and joint pain and nausea seemed to be related to factors external to SARS-CoV-2 infection. In most cases, long COVID complaints resolved within 1–5 months.

Another national study compared 6630 adolescents with PCR-confirmed SARS-CoV-2 (case group) with 21 640 matched controls [49▪▪]. Participants in the case group had greater odds of having at least one COVID symptom lasting at least 2 months but reported less somatic distress and better quality-of-life scores than the control group. The case group had more sick days and more school absences than control individuals.

Stephenson *et al.* [50] found that nearly all symptoms reported by children who tested positive for SARS-CoV-2 were also reported by those who tested negative. Moreover, no difference was seen between the two samples in mental health, overall wellbeing or impairment of activities.

A Norwegian registry-based cohort study revealed that COVID-19 among children and adolescents had limited impact on healthcare services. Preschool age children tended to take longer (3–6 months) to recover than primary or secondary school students (1–3 months), usually because of respiratory conditions [51▪].

Altogether, the published studies do not resolve the uncertainty around the true prevalence of long COVID in children. The research agenda calls for further analyses that distinguish better symptoms caused by SARS-CoV-2 from pandemic-related complaints and enroll appropriate control groups,

including children with other infections or hospitalized for other reasons.

## CONCLUSION

Although COVID-19 had a relatively limited impact on children and adolescents, pediatric specialists have been faced with a broad range of SARS-CoV-2-related clinical manifestations and with the occurrence of a novel postinfectious hyperinflammatory syndrome with characteristics similar to Kawasaki disease. After more than 2 years, since the first report of MIS-C, a large experience has been gained, which will help to recognize it timely and to treat it appropriately. However, further studies of the pathophysiology of MIS-C are needed to develop more targeted therapies and to clarify its relationship with Kawasaki disease. These investigations will provide an important opportunity to understand the etiopathogenesis of Kawasaki disease and of other inflammatory disorders whose causative factors and mechanisms are still elusive. A global multidisciplinary effort of healthcare services is required to determine the exact burden and duration of post-COVID problems in the young age group.

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*There are no conflicts of interest.*

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# Biologic disease-modifying antirheumatic drugs to treat multisystem inflammatory syndrome in children

*Randy Q. Cron*

**Purpose of review**
Multisystem inflammatory syndrome in children (MIS-C) is a postinfectious complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection primarily affecting children. MIS-C shares features with Kawasaki disease (KD) and cytokine storm syndrome (CSS) frequently requiring intensive care support. Although intravenous immunoglobulin (IVIg) and glucocorticoids (GCs) are effective therapeutics for most, refractory MIS-C is treated with various biologic disease-modifying antirheumatic drugs (bDMARDs). Understanding the clinical features, inflammatory cytokines, and genetic associations provides rationale for bDMARD in treating severe MIS-C.

**Recent findings**
Children with MIS-C have clinical KD features and often present in hypovolemic and cardiogenic shock requiring volume repletion (gastrointestinal losses) and cardiac pressor support (epinephrine). Investigation of MIS-C serum reveals elevated pro-inflammatory cytokines [interleukin (IL)-1, IL-6, IL-18, interferon gamma (IFNγ), tumor necrosis factor (TNF)], but to a lesser extent than other established CSS. Gene sequencing of MIS-C children identifies heterozygous mutations in CSS associated genes. Treatment of refractory (IVIg and GC) MIS-C with bDMARDs to IL-1, IL-6, and TNF is efficacious for survival as well as resolving cardiac and coronary artery inflammation.

**Summary**
MIS-C is a postinfectious complication of SARS-CoV-2 resembling KD and CSS, both genetically and by pro-inflammatory cytokines. MIS-C that is refractory to IVIg and GC is routinely responsive to bDMARDs targeting IL-1, IL-6, and TNF.

**Keywords**
biologic disease modifying antirheumatic drug, cytokine storm syndrome, intravenous immunoglobulin, Kawasaki disease, multisystem inflammatory syndrome in children

## INTRODUCTION

As pediatricians, we were initially grateful that children were largely spared severe manifestations of coronavirus disease 2019 (COVID-19) associated with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic [1]. However, to everyone's surprise an increase in what appeared to be cases of Kawasaki disease (KD) were being reported in children in Europe [2,3▪▪], and soon after in the northeastern United States [4▪,5▪], approximately a month after COVID-19 blossomed in the respective regions of the planet. Although different terminologies were used to describe this novel disease entity (e.g. pediatric multisystem inflammatory syndrome or PMIS; multisystem inflammatory syndrome in children or MIS-C), it appeared to be largely restricted to previously healthy children and a few young adults (MIS-A) [6]. Definitions for MIS-C were established early on, and the United States Centers for Disease Control and Prevention (CDC) definition was as follows: under 21 years of age, fever, laboratory evidence of inflammation, severity requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic,

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## KEY POINTS

- Multisystem inflammatory syndrome in children (MIS-C) is a postinfectious illness resembling severe Kawasaki disease (KD) that affects a small subset of children previously infected with severe acute respiratory syndrome coronavirus 2 approximately 1 month earlier.
- Like KD, children with MIS-C can develop coronary artery dilation and aneurysms, as well myocarditis and cardiogenic shock.
- Heterozygous mutations in known familial hemophagocytic lymphohistiocytosis genes (e.g. *PRF1*, *UNC13D*) have been identified in children with MIS-C, similar to what has been reported in other cytokine storm syndrome (CSS) cohorts, and may serve as risk alleles.
- MIS-C lies along the spectrum of CSSs, and serum from children with MIS-C contains elevated levels of CSS-associated pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF).
- MIS-C typically responds to immunoglobulin and glucocorticoids, but biologic disease-modifying antirheumatic drugs therapeutics targeting IL-1, IL-6, and TNF have proven valuable for treating refractory MIS-C.

or neurologic) and no alternative plausible diagnoses and positive for current or recent SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR), serology, or antigen test; or COVID-19 exposure within 4 weeks of symptom onset [3▪▪,7].

Clinically, MIS-C appeared to effect younger children differently than adolescents, but with overlapping features in both populations. Younger children, particularly those under 5 years of age, presented much like KD with fever, mucocutaneous involvement, and risk for coronary artery abnormalities [4▪,5▪]. Other cardiovascular features included carditis (with decreased ejection fractions) and pericarditis [4▪,5▪]. In addition, over 90% of children of all ages with MIS-C suffered gastrointestinal involvement with nausea, vomiting, and diarrhea [4▪,5▪]. The combination of cardiovascular dysfunction and gastrointestinal fluid losses, particularly in the teenage population, frequently resulted in a state of shock requiring intensive care with intravenous volume repletion and vasopressor support (e.g. epinephrine). Some children even required invasive mechanical ventilation and occasionally extracorporeal membrane oxygenation (ECMO). Some of these children also had features of a cytokine storm syndrome [8], and early mortality rates for MIS-C ranged from 1 to 2% [4▪,5▪], in the range of severe COVID-19 for adults.

Because of the shared features with KD, and the risk of coronary artery dilation and aneurysms, therapy for KD was utilized for MIS-C early on. This included intravenous immunoglobulin (IVIg) to prevent coronary changes, low dose aspirin (ASA) for coronary artery clot reduction, and glucocorticoids (GCs) to dampen inflammation in more severe disease [3▪▪,9▪▪]. Despite the severity of illness at presentation, the vast majority of children responded rapidly to this approach. Some centers reported an average length of hospital stay of 5 days for children with MIS-C, notably shorter than the small subset of children (mostly those with prior underlying health conditions like diabetes, neurodevelopmental disorders, obesity, etc. – similar to adults) with active SARS-CoV-2 infection hospitalized for severe COVID-19 (14 days mean stay) [10]. For those children with MIS-C refractory to IVIg and GCs, other biological disease modifying antirheumatic drugs (bDMARDs) were found to be effective (Table 1). These bDMARDs included agents targeting pro-inflammatory cytokines including interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) [3▪▪,9▪▪,11▪▪,12]. This review will cover the pathophysiologic rationales for employing bDMARDs to treat MIS-C, as well as their benefit.

## PATHOPHYSIOLOGY OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Although MIS-C was a surprise to the world during the early phase of the SARS-CoV-2 pandemic, there had been previous coronavirus outbreaks associated with KD-like illness [13]. This led some to suggest that KD should be considered a syndrome, rather than a disease, that can potentially result from several infectious or environmental triggers [14]. The fact that the peak of MIS-C cases occurred approximately one month following the peak of COVID-19 in various geographic outbreaks, combined with the presence of SARS-CoV-2 antibodies

**Table 1.** Biologic DMARD therapies used to treat MIS-C

| bDMARD | Mechanism of action |
|---|---|
| IVIg | Multiple – broadly immunomodulatory |
| Anakinra | Recombinant IL-1 receptor antagonist |
| Infliximab | Monoclonal antibody to TNF |
| Tocilizumab | Monoclonal antibody to IL-6 receptor |

DMARD, disease-modifying antirheumatic drug; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children.

and frequently negative RT-PCR evidence of ongoing infection, suggested that MIS-C was a post-infectious process. Even when PCR evidence of the virus was detected in children with MIS-C, the viral burden (perhaps residual viral nucleic acid) was exceeding low (e.g. required high PCR cycle numbers for detection) [15▪▪]. Thus, therapy focused quickly on dampening the hyper-inflammatory immune response rather than antiviral approaches. A recent report suggested that the combination of IVIg, a traditional biologic agent, with GCs is associated with a lower risk of new or persistent cardiovascular involvement than IVIg alone [16▪▪]. This likely bespeaks to the severe inflammatory state associated with MIS-C and its inclusion under the broad cytokine storm syndrome (CSS) umbrella [17].

The prototypic CSS is familial hemophagocytic lymphohistiocytosis (fHLH) which typically presents in infancy as a result of largely homozygous (autosomal recessive) genetic defects in genes critical to the perforin-mediated cytolytic pathway employed by cytotoxic lymphocytes ($CD8^+$ T cells and natural killer (NK) cells) [18]. Absent or delayed killing of virally-infected antigen presenting cells (APC) not only results in viral persistence (the trigger in genetically susceptible hosts) but in prolonged interaction between the cytolytic lymphocyte and the APC. This prolonged engagement resulting from defective cytolysis yields increased pro-inflammatory cytokine production (e.g. TNF, IFNγ) believed to contribute to the multi-organ system failure of CSS [19–21]. As fHLH is rare (1 in 5000 live births), heterozygous hypomorphic [22] or dominant-negative defects in fHLH genes [21,23] are believed to contribute to the much more common secondary forms of HLH [24] through a threshold model of disease [25]. There has even been evidence for fHLH heterozygous gene defects serving as a risk factor for developing severe COVID-19 [26,27▪] similar to what has been reported for H1N1 influenza [28].

Few studies have explored genetic contributions as to why some children go on to develop MIS-C while most infected with SARS-CoV-2 do not. Recently, heterozygous defects in immune related genes (e.g. *TLR3*, *IFNB1*) were identified among a cohort of MIS-C children from the Middle East [29]. Previously, haploinsufficiency in *SOCS1* (suppressor of cytokine signaling 1) was reported in children with MIS-C [30▪]. The same group of investigators also identified a boy with MIS-C possessing a missense mutation in the X-linked gene *XIAP* [31▪]. Intriguingly, mutations in *XIAP* are established risk factors for HLH development [32]. Similarly, a toddler with MIS-C was found to have homozygous defects in the fHLH gene *STX11* [33]. Along these lines of reason, a recent cohort of 39 children with MIS-C was explored for fHLH gene mutations, and 25% possessed heterozygous mutations in traditional HLH genes (*LYST*, *STXBP2*, *PRF1*, *UNC13D*, *AP3B1*) and *DOCK8* [34▪], a newly proposed HLH gene [18,34▪,35]. Thus, genetic defects in HLH genes may serves as risk alleles for developing the CSS associated with MIS-C (Table 2).

**Table 2.** HLH associated gene associations in children with MIS-C

| Familial HLH gene | Role in perforin-mediated cytolytic activity |
|---|---|
| *PRF1* | Pore formation in target cell allowing for granzyme delivery and apoptosis |
| *UNC13D* | Vesicle priming |
| *STX11* | Vesicle docking |
| *STXBP2* | Vesicle membrane fusing |
| *LYST* | Vesicle sorting |
| *AP3B1* | Vesicle trafficking |
| *DOCK8* | GTPase important for vesicle movement along actin cytoskeleton |
| *XIAP* | Inflammasome related |

HLH, hemophagocytic lymphohistiocytosis; MIS-C, multisystem inflammatory syndrome in children.

The clinical and laboratory features of CSS were present in studied cohorts of children with MIS-C; however, the severity of many of the laboratory features detected in the blood did not reach the extent of elevation as seen in more traditional CSS, like macrophage activation syndrome (MAS) [7,36]. While markers of CSS/MAS, including sCD25, ferritin, IL-18, and CXCL9 (indirect correlate with interferon-gamma (IFNγ)), were elevated in children with MIS-C, the degree of elevation was typically a log or more less than detected in children with other causes of CSS/MAS [9▪▪]. The initial reports evaluating the cytokine milieu in children with MIS-C identified IL-1β, IL-6, IL-10, TNF, and IFNγ as cytokines elevated in the serum of children with MIS-C [9▪▪,15▪▪]. Whereas IL-10 is a regulatory cytokine likely representing the body's attempt to dampen the ongoing hyper-inflammatory state, the other elevated cytokines are all targetable with currently available bDMARDs [32]. Recently, it was reported that patients with MIS-C and HLH both show robust T cell activation with elevated T-helper-1 (Th1) and pro-inflammatory cytokines, including IFNγ [37▪]. Again, the amplitude of cytokinemia was higher in HLH than MIS-C, and MIS-C patients also had a distinguishing feature of elevated Th2 cytokines such as IL-4 and IL-13 [37▪]. Fortunately, these immune parameters were resolved at MIS-C

follow-up visits [37▪]. Thus, although not identical to HLH, MIS-C patients share a hyper-inflammatory phenotype providing rationale for biologic therapeutics targeting pro-inflammatory cytokines.

## BIOLOGICAL DISEASE-MODIFYING ANTIRHEUMATIC DRUG USE IN MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Decades ago, IVIg was shown to dramatically reduce the incidence of coronary artery abnormalities in children with KD, and is considered a mainstay of therapy for MIS-C [38▪▪]. The mechanism of action of IVIg in treating hyper-inflammation is multifactorial, including blockade of Fc receptors on phagocytic cells, neutralization of cytokines by specific antibodies, complement inhibition, alterations of regulatory T cells, and many others [39]. There are likely multiple mechanisms involved, and IVIg is often used to treat secondary HLH, particularly when triggered by infection [40]. Since MIS-C shares many features with KD, including coronary artery derangements, IVIg has been standard first-line therapy for children hospitalized with MIS-C [38▪▪]. IVIg has largely been effective at treating MIS-C [41], but the addition of GCs to IVIg has been reported to lower the risk of new or persistent cardiovascular dysfunction compared to IVIg alone [16▪▪]. Nonetheless, a small subset of children with MIS-C may require additional anti-inflammatory approaches, including targeting of pro-inflammatory cytokines with bDMARDs.

Not knowing which bDMARDs will be effective in treating IVIg and GC refractory MIS-C, initial approaches used anticytokine therapies employed in refractory KD and other secondary HLH [42]. The use of IL-1 inhibition with anakinra (recombinant IL-1 receptor antagonist) was explored early during the pandemic to treat refractory MIS-C [3▪▪,9▪▪,11▪▪,12]. Anakinra was also selected for its rapid and high benefit to side-effect ratio [43]. Additionally, anakinra has a short half-life and a wide therapeutic dosing range making it an attractive therapeutic for CSS [44]. Anakinra has been reported to be highly efficacious in treating many secondary HLH patients [45,46], and even a case of familial HLH [33]. Moreover, anakinra has anecdotally been reported to treat severe refractory KD [47], and anakinra is undergoing clinical trials for children with KD coronary artery aneurysms [48]. The shared features between KD and MIS-C, along with anakinra's reported benefits in treating MIS-C, have resulted in anakinra being recommended as an option for MIS-C refractory to IVIg and CS in the latest version of the American College of Rheumatology (ACR) MIS-C clinical guidance treatment algorithm [38▪▪].

The other therapeutic bDMARD option listed in the most recent ACR MIS-C clinical guidance for refractory MIS-C algorithm is infliximab [38▪▪]. Infliximab is a monoclonal antibody (mAb) directed against TNF, another pro-inflammatory cytokine implicated in CSS [49]. Perhaps, more relevant, infliximab has proven beneficial in treating refractory KD, even more so than a second dose of IVIg [50▪]. Thus, early during the pandemic, infliximab was explored for treatment of refractory MIS-C [3▪▪,11▪▪]. Anecdotally, a clinical case series has reported benefit with infliximab used to treat a dozen children with MIS-C [51]. Fortunately, many children with MIS-C and coronary artery dilation and aneurysms resolve coronary abnormalities as detected by cardiac echocardiogram during outpatient hospital follow-up visits [52▪]. These studies have included children with MIS-C treated with anakinra, inflixamb, and the anti-IL-6 receptor mAb tocilizumab [52▪].

IL-6 is yet another pro-inflammatory cytokine implicated in the pathogenesis of various CSSs [49]. The bDMARD tocilizumab, which blocks IL-6 signaling, garnered a lot of attention early during the COVID-19 pandemic, as IL-6 was noted to be elevated in the serum of severe COVID-19 patients [53]. Early reports suggested tociliuzumab treatment helped severe COVID-19 patients, and meta-analyses have demonstrated some benefit to those with severe COVID-19 pneumonia [54,55]. As soon as MIS-C was recognized as a SARS-CoV-2-associated illness, tocilizumab was also explored as a therapeutic option for children with refractory MIS-C [11▪▪,12]. Tocilizumab has been reported in case series to benefit children with MIS-C experiencing cardiogenic shock [56,57]. Tocilizumab has a track record in treating various CSS, and it has the United States Food and Drug Administration (FDA) approval to treat cytokine release syndrome associated with chimeric antigen receptor T cell therapy for refractory leukemia and lymphoma [58].

Another recent FDA approval for CSS is the anti-IFNγ mAb emapalumab demonstrated to benefit infants with fHLH [59▪]. Like IL-1, IL-6, and TNF, IFNγ is also elevated in the serum of children with MIS-C [9▪▪,15▪▪]. In part, as this therapeutic is not readily available, there has been little exploration of its role in MIS-C. Nonetheless, IFNγ is a central cytokine in many CSS scenarios, and blockade with emapalumab may theoretically benefit children with refractory MIS-C. Another CSS-associated pro-inflammatory cytokine found to be elevated

in MIS-C is the IL-1 family member IL-18 [9▪▪,60]. Like IL-1, IL-18 has a natural inhibitor, IL-18 binding protein that, like anakinra, is a therapeutic agent, takedinig alfa. Takedinig alfa has been used to successfully treat a CSS in a child with an autoinflammatory condition resulting from a dominant mutation in *NLRC4* [61]. Hypothetically, IL-18 blockade may also be of benefit to children suffering refractory MIS-C. Whether targeting IFNγ, IL-18, or other pro-inflammatory cytokines elevated in MIS-C (e.g. IL-17) will benefit children with refractory MIS-C remains unclear. Fortunately, despite a reported ∼1.5% mortality rate, outcomes have been very favorable for treating refractory MIS-C using the currently tested bDMARDs that block IL-1, IL-6, and TNF [56,62–64].

## CONCLUSION

Who would have predicted the MIS-C scourge when COVID-19 began circling the globe [7]? This postinfectious hyper-inflammatory illness of children with features of KD, including coronary artery dilation, presents acutely approximately one month following an asymptomatic or symptomatic SARS-CoV-2 infection in a small subset of children. There are likely genetic risk factors for why some children develop this and most do not, including mutations in genes associated with fHLH and other CSSs. While MIS-C is not identical to MAS and other CSSs, serum from children with MIS-C possess elevated levels of pro-inflammatory cytokines, including IL-1, IL-6, and TNF. Fortuitously, bDMARDs that target these cytokines are useful adjunctive life-saving therapies for children with MIS-C refractory to IVIg and GCs leading to favorable outcomes.

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### Conflicts of interest

*Dr Cron reports speaker fees, consulting fees, and grant support from Sobi, consulting fees from Sironax and Novartis, speaker fees from Lilly, and clinical trial side-effect adjudication committee work support from Pfizer.*

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# Osteoporosis epidemiology using international cohorts

*Mattias Lorentzon*[a,b,c] *and Bo Abrahamsen*[d,e,f]

**Purpose of review**
To provide an update on the most important new cohort studies within osteoporosis and their bearing on clinical management and directions for future research.

**Recent findings**
We identified a collection of new observational cohort studies - including new reports from already established large cohorts - and intervention studies providing new insights into osteoporosis pathophysiology, risk finding, intervention, and treatment barriers.

**Summary**
Recent cohort studies in osteoporosis highlight the importance of timely identification and treatment of people who are at high risk of suffering osteoporotic fractures. Physical performance is a strong indicator of fracture risk and one that is tightly linked to a number of chronic conditions, not least inflammatory conditions like rheumatoid arthritis. Advances in case finding may involve opportunistic screening for low bone mineral density and vertebral fractures of radiology images obtained for other purposes, polygenic risk scores, and routinely collected medication and comorbidity information.

**Keywords**
cohort studies, falls, fracture epidemiology, nutrition, osteoporosis

## INTRODUCTION

Clear insights into how osteoporotic fractures can be predicted and averted are paramount if we are to succeed in reducing the global fracture burden against a backdrop of an increasingly elderly population in industrialized nations. Cohort studies are particularly important sources of such information and the purpose of this narrative review is to summarize the key such studies that have been published in the last year, set them into context and propose directions for future research.

## NEW STUDIES ON OSTEOPOROSIS PATHOPHYSIOLOGY

Cohort studies are essential tools in identifying factors that contribute to the failure of building an adequate bone mass in adulthood or in maintaining bone mass later in adult life. In general, this requires long follow-up in large cohorts. The studies reported under this heading are all observational studies while intervention studies are reviewed below. Important new studies in the past year have addressed genetic influences on bone mineral density (BMD) and fracture risk, hormonal, nutritional, lifestyle, and environmental factors (Table 1). Three new well-powered longitudinal studies of food patterns are worthy of particular attention. Most notably, a study in more than 25 000 British adults followed for a mean of almost 18 years [1▪▪] found a significantly higher fracture risk in persons with the highest quintile of dietary acid load compared with the lowest quintile. A secondary analysis of a Mediterranean diet trial in subjects at increased risk of ischemic heart disease (IHD) also confirmed a relationship between dietary acid load and the risk of fractures but in this patient group the relationship was more compatible with a U-shaped relationship with the mid tertile being

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## KEY POINTS

- Timely identification and treatment of persons who are at high risk of fracture is key to reducing societal and individual fracture burden and this risk is in part attributable to physical function and chronic medical conditions.
- Imminent fracture risk is recognized as important for targeting cost effective intervention yet remains somewhat poorly understood as a concept.
- New tools to help close the treatment gap include automated case finding with opportunistic identification of vertebral fractures and low BMD, as well as using information already available in electronic health records and/or introduction of polygenic risk scores.

at lowest risk [2]. Further, an Australian cohort study found lower annual loss rates for hip BMD in people with high Western or Animal Protein diet scores [3]. An interesting new study from Korea reported a significantly higher risk of osteoporosis in subjects who had blood cadmium levels above the median [4] - the authors speculate that conversion of 25OHD to 1,25OH2D could be disturbed by cadmium.

Given the importance of mechanoreceptors for regulating local bone remodelling one would expect that activities with different anatomical loading to result in site specific changes in BMD that could lead to differences in fracture risk in the long term. Such site-specificity was recently confirmed in a study of more than 300 000 women in the UK followed for 12 years [5▪▪].

As regards hormonal influences, potent topical glucocorticoids used in treating skin conditions have been found to be associated with a dose dependent increase in major osteoporotic fractures in a large analysis using the Danish prescription database [6▪▪]. For endogenous glucocorticoids, a very long-term analysis in a limited number of patients who were cured for Cushing's Syndrome revealed a slow recovery in BMD following cure with increases seen as late as 20 years after diagnosis and

**Table 1.** Pathophysiology

| Pathophysiology aspect | Study | Population | Key findings |
|---|---|---|---|
| Physical activity | Armstrong *et al.* (2020) [5▪▪] | 371 279 UK women mean age 59.8 years followed for 12 years (mean). | Effects on fracture risk are site- and activity specific. Walking, gardening, yoga, and sports reduced risk of hip fracture, house work reduced the risk of ankle fractures, cycling increased the risk of forearm fractures. Most effect sizes small apart from sports and hip fracture (0.78(0.71, 0.87)) and gardening and forearm fracture (0.76(0.66, 0.89)). |
| Stroke, disability, and fracture risk | Northuis *et al.* (2020) [17] | In total, 4640 postmenopausal women, 50-79 years, who survived a stroke during follow-up in the Women's Health Initiative study ($n = 161\,808$). | The risk of hip fracture was more than doubled (Hazard ratio 2.1 (95% confidence interval) 1.4–3.2) in those with severe disability at discharge after stroke, while the risk was not increased in those with moderate disability (hazard ratio 1.1 (95% confidence interval) 0.7–1.7). |
| Parkinson's disease prodromal phase and fracture risk | Camacho-Soto *et al.* (2020) [18] | 89 632 patients with Parkinson's disease and 117 760 controls, 66–90 years old. The 5-year prodromal period was investigated. | Compared to controls, the risk of any fracture was increased in the period within 3 months from PD diagnosis (Odds Ratio (OR) 3.04 (95% confidence interval) 2.85–3.05), but also 3–4 years (OR 1.36 (95% confidence interval) 1.29–1.43) before diagnosis. |
| Rheumatoid arthritis | Erwin *et al.* (2021) [9▪▪] | 147 143 UK adults aged >= 18 in CPRD 1992 to 2016. | Increased fracture risk in rheumatoid arthritis, including patients under fifty years of age. Statistically significant in women <50 (IRR 1.29 confidence interval 1.12–1.49) but not in men <50. |
| | Theander *et al.* (2020) [10▪] | 220 Swedish patients with early rheumatoid arthritis followed for 5-10 years. | Reduced femoral neck BMD in men but not women at the time of diagnosis. Further, men had a 6.9% decline in BMD during the first five years while this was not seen in women. Men had more treatment with glucocorticosteroids, were less likely to receive qntiosteoporotic treatment and had more erosions at baseline though this did not appear to explain the difference. |

**Table 1** (*Continued*)

| Pathophysiology aspect | Study | Population | Key findings |
|---|---|---|---|
| Dietary acid load | García-Gavilán *et al.* (2021) [2] | Secondary analysis of Mediterranean diet trial in 870 Spanish men and women, mean age 67 years, with high risk of IHD. | Lower fracture risk in the mid tertile(T1) of PRAL, which was selected as the reference group. Multivariable adjusted fracture risk hazard ratio 1.83 (1.08, 3.09) in T1 and hazard ratio 1.87 (1.10, 3.17) in T3. |
| | Hayhoe *et al.* (2020) [1▪▪] | 25 438 community living UK adults aged 39–79 years in the EPIC-Norfolk cohort, mean f-u 17.9y. | Overall increased osteoporotic fracture risk in highest PRAL quintile compared with lowest. Men 1.33 (95% confidence interval: 1.03–1.72) and women 1.21 (95% confidence interval: 1.03–1.42). |
| Food patterns | Nguyen *et al.* (2021) [3] | Community living Australian adults ($N = 1098$, aged $\geq$50 years) invited through electoral roll. | Fruit and vegetable food pattern associated with reduced falls risk at baseline but there was no difference in fracture risk. Marginal nonsignificant risk increase with higher Animal Protein(AP) score RR 1.13 (0.99, 1.28). Annual decreases of FN and hip BMD were less for higher Western or AP pattern scores. |
| Corticosteroids, dermal | Egeberg *et al.* (2021) [6▪▪] | 723 251 Danish adults, mean age 52.8 years, treated with the equivalent of at least 200 g of mometasone. | Dose dependent increase in risk of MOF. hazard ratio 1.01 (95% confidence interval, 0.99–1.03) for exposure to 500 to 999 g, 1.05 (95% confidence interval, 1.02–1.08) for exposure to 1000 to 1999 g, 1.10 (95% confidence interval, 1.07–1.13) for exposure to 2000 to 9999 g, and 1.27 (95% confidence interval, 1.19–1.35) for exposure to at least 10 000 g. NNH 454 person-years with exposure of 10 000 g or higher. |
| Corticosteroids, endogenous | Van Houten *et al.* (2021) [7] | Clinic cohort of 231 Dutch patients with Cushing's syndrome using data collected between 1960 and 2020. A total of 80 had follow-up BMD measurements. | Improvements In lumbar spine BMD but not femoral neck BMD were seen at the 20 year point ($n = 37$). Vertebral fracture rates were at their highest in the two years before treatment and declined thereafter. |
| Sex hormones | Yeap *et al.* (2020) [8] | Cohort of 3307 community-dwelling Australian men aged $76.8 \pm 3.5$ years followed for 10.6 years. | Plasma total testosterone was associated with fracture risk (any and hip) in a U-shaped relationship with no association with DHT, E2, and LH. Lowest hip fracture risk was seen at total testosterone levels between 10 and 15 nmol/L. Higher SHBG levels were associated with higher hip fracture risk (Q4 vs. Q1 hazard ratio 1.76, $P = 0.033$). |
| Blood cadmium levels | Kim *et al.* (2021) [4] | Random sample of 5432 participants in the 4th and 5th Korean National Health and Nutrition Examination Survey. Cross-sectional BMD. | Prevalence of osteoporosis in unadjusted models significantly higher in Q3 and Q4 with Q1 as reference. In adjusted models Q2 1.54 (1.05–2.25), Q3 3.63 (2.31–5.69), Q4 1.70 (1.03–2.81). |
| Loss-of-function mutations | Surakka *et al.* (2021) [11] | 19 705 Norwegian participants in the Nord-Trøndelag Health Study, using initial low-pass whole genome sequencing. | LoF mutation in MEPE, p.(Lys70IlefsTer26) with minor allele frequency 0.8% linked to 0.5 SD lower forearm BMD and higher prevalence of fractures (OR 1.35 [1.18; 1.54]). |

treatment [7]. By contrast, vertebral fracture risk decreased quickly. Since no increase was seen in hip BMD it is possible that spinal osteoarthrosis may have influenced the BMD trajectory in this noncontrolled cohort study.

For male osteoporosis, the relative contributions of male and female sex hormones remain controversial. New cohort findings from Australia [8] support a key role of total testosterone and SHBG as opposed to estradiol but more work is needed.

Within inflammatory causes of bone loss, UK register data report increased fracture risk in women with rheumatoid arthritis, including the age group under 50 [9▪▪]. Conversely, DXA data in Swedish patients with rheumatoid arthritis found low BMD to be more common in men than women and that male rheumatoid arthritis patients experienced a further BMD decline in the first years after diagnosis while this was not observed in women [10▪].

Finally, analysis for loss-of-function mutations in a Norwegian cohort identified a mutation in the MEPE gene in 0.8% of the population, which was linked to a 0.5 SD average forearm BMD and increased fracture risk [11]. Other mutations in this gene are known lead to cranial bone defects and to otosclerosis but a link to osteoporosis has not been suspected in the past.

## NEW STUDIES ON PREDICTION OF FRACTURE RISK

Several new reports have addressed imminent (i.e. short term, 1-2 years) fracture risk using new or previously collected cohort data. This area of research has come very much into focus with the development of fast acting anabolic therapies with a case for directing such treatment to those at high short term risk, whereas the long-term scenario could be adequately served by slower acting medication. Since imminent fracture risk is known to be particularly high in postfracture period, Iconaru *et al.* [12] used the FRISBEE cohort to identify risk factors for imminent fracture in the postfracture period in 3560 postmenopausal women and found that fractures of the spine, pelvis, hip, scapula, clavicles, and proximal humerus ('central fractures') were more strongly associated with subsequent imminent fracture risk than 'major osteoporotic fractures' (MOF). The importance of age, osteoporosis, and comorbid conditions was confirmed. In another cohort study [13], a risk algorithm for imminent fractures was built and tested using a split Medicare sample. In brief, a simplified model with age (up to seven points), race (up to 7 points) and four binary predictors (falls 3 points, psychotropics 4 points, recent fracture 10 points and female gender 4 points) had a c-statistic of 0.71.

The mechanisms explaining the increased imminent risk following a prior fracture are incompletely understood. New analyses of data from the Study of Osteoporotic Fractures (SOF) [14] and the Canadian Multicentre Osteoporosis Study [15] have provided new insights into the theoretical pathways explaining increased fracture risk. In SOF, age was found to influence risk through effects on general health and physical functioning, with prior fracture, low BMD, falls, and poor physical functioning statistically contributing directly to 1-year nonvertebral fracture risk. A series of path diagrams are provided in the paper. The findings in CaMOS were largely in agreement with those of SOF. However, CaMOS data were more compatible with falls acting not directly on risk but being indicative of poorer functioning and poorer general health. On a similar note, but outside the imminent risk scenario, prospective data from the Dubbo Osteoporosis Epidemiology Study that showed that the rate of decline in physical performance was an independent predictor of fracture in both genders [16]. This ties in well with recent findings from the WHI study, where 4640 women, aged 50–79 years, suffered from a stroke during follow-up [17]. The risk of hip fracture was more than doubled in those with severe disability at discharge after stroke. Similarly, in a cohort of 89 632 patients with Parkinson's disease and 117,760 controls, the risk of fracture was higher in the time period within 3 months before Parkinson's disease diagnosis [odds ratio (OR) 3.04 (95% confidence interval, CI) 2.85–3.05] but also elevated in the period 3–4 years [OR 1.36 (95% CI) 1.29–1.43] before diagnosis[18].

Finally, new HR-pQCT data from the OFELY and QUALYOR cohorts [19] demonstrating the importance of distal radial structural parameters in predicting fractures in postmenopausal women with normal BMD or osteopenia, a group accounting for 80% of fractures in the study. The authors suggest that implementation of this tool may be cost-effective. In the SWAN cohort, the subsequent risk of fractures was 27% greater for each one SD increment in bone turnover markers during the menopausal transition. The authors advocate for trials of early short-term antiresorptive therapy in women with the highest BTM increase at menopause [20]. Finally, targeting BMD measurements or intervention by a new polygenic risk score was proposed in a study using subcohorts of the UK Biobank with a potential for reducing the need for risk stratification by DXA [21].

## NEW STUDIES ON REDUCING THE TREATMENT GAP

Important cohort studies focusing on aspects of reducing the treatment gap have recently been published (Table 2). The increased risk following an index fracture is not linear, but how the second or third fracture affect the risk of further fracture is less studied. In a cohort of Swedish women with at least one fracture, the cumulative 5-year incidence of subsequent MOF was higher after the second than after the first fracture (32% and 21%, respectively) [22▪▪]. An analysis based on 9504 Icelandic men and women with sentinel osteoporotic fracture [23]

**Table 2.** Barriers to treatment

| Barrier aspect | Study | Population | Key findings |
|---|---|---|---|
| Fracture risk and implementation of fracture liaison services in western Sweden. | Axelsson *et al.* (2020) [24▪▪] | 21 083 patients with recent fracture at two hospitals with FLS and two without, in western Sweden. | All patients ($n=13\,946$) with a fracture during the FLS period were compared with all patients in the period prior to FLS start ($n=7137$) using an intention-to-treat analysis. The risk of recurrent fracture was lower in the FLS period compared with the control period (hazard ratio 0.82, (95% confidence interval) 0.73–0.92), corresponding to a 3-year number needed to screen of 61. |
| Cost-effectiveness of fracture liaison services. | Senay *et al.* (2021) [25] | 532 patients were followed in an FLS in Canada (mean age 63 years, 86% women). | The rates of investigation, treatment, and medication persistence were higher in the FLS than in usual care. In the FLS, compared to usual care, the ICURs for the high followers, intermediate followers, and low followers $4250, $21 900, and $72 800 per quality-adjusted life year gained, respectively, indicating that a high-intensity FLS can be cost-effective. |
| Risk of subsequent fracture after first, second and third fracture. | Sreskog *et al.* (2020)[22▪▪] | 231 769 Swedish women, 50 years or older, with at least 1 fracture. | The cumulative incidence of subsequent major osteoporotic fracture (MOF) was higher in patients with fracture than in controls (one previous fracture: 20.7% vs. 12.3%; two previous fractures: 32.0% vs. 15.3%) after 5 years. The risk of subsequent MOF was highest within the first 24 months after an index fracture. |
| Alendronate medication possession ratio and risk of second hip fracture. | Chen [26] | 38 675 patients from Taiwan with an index hip fracture, were included, of which 52.7% were women, and 80% of patients were without alendronate medication. | 2392 patients had a second hip fracture, and the incidence was 1449/100 000 person-years. Patients with alendronate medication possession ratio (MPR) of 50–75% had a lower risk of a second hip fracture compared to nonusers (hazard ratio 0.66 (95% confidence interval) 0.49–0.88). Alendronate treatment with MPR lower than 50% was not associated with lower risk of hip fracture. |
| Timing of antiosteoporosis medications initiation after a hip fracture risk of fracture. | Wang *et al.* (2020) [27▪] | 77 930 patients with hip fracture, of which 9986 were prescribed antiosteoporotic medications (AOM) in Taiwan. | Delayed AOM initiation to 252 days after hip fracture was associated with an increased risk of fracture-related hospitalization (hazard ratio 1.93 (95% confidence interval) 1.29–2.89), compared to AOM initiation after 18–84 days. |
| Deep learning of lumbar spine X-ray for screening for osteopenia and osteoporosis. | Zhang *et al.* (2020) [29] | 808 postmenopausal women, 50–92 years old, from three tertiary centres in China. | A 3-class deep convolutional neural network model was trained to classify normal bone density, osteopenia and osteoporosis using lumbar spine X-ray images, as compared to a DXA-based classification. In test dataset 1, area under the curve (AUC) was 0.767 (95% confidence interval) 0.70–0.82) diagnosing osteoporosis and in dataset 2 AUC was 0.726 (95% confidence interval) 0.65–0.80). |
| Factors associated with osteoporosis therapy decisions. | Kline *et al.* (2021) [28] | 64,181 women, of whom 33.8% started osteoporosis medication, in Manitoba, Canada. | A T-score $\leq$ -2.5 was associated with the highest OR for treatment (OR 7.59 (95% confidence interval) 7.19–8.01). A high FRAX score was associated with lower odds of therapy (OR 0.80 (95% confidence interval) 0.74–0.88. |

found that the risk of subsequent fracture was highly dependent on fracture type, with hip and spine fractures conferring the highest risk, and patient age, with increasing relative risk with decreasing age. The rates of subsequent fracture after an index MOF, before and after fracture liaison service (FLS) implementation was investigated in a cohort study of 21 083 patients, at two hospitals with FLS implementation and two without, in western Sweden. The risk of recurrent fracture was 18% lower in the FLS period compared with the control period, with a corresponding number needed to screen of 61 in

3 years to prevent a fracture. In the hospitals without FLS implementation, no change in recurrent fracture rate was observed, providing strong support for a causal effect of the FLS in reducing recurrent fracture rates [24▪▪]. As reported from a Canadian FLS, the rates for investigating, treatment, and persistence with osteoporosis medication were higher in the FLS than in usual care. It was concluded that the whole FLS was cost-effective in 67% of the simulations [25], further advocating the usefulness of this type of care pathway.

Medication initiation is an essential component of a successful FLS. The importance of timing and persistence of treatment after hip fracture was addressed in two recent studies. In a large cohort of patients with hip fracture in Taiwan, only patients with an alendronate medication possession ratio 50% or higher had lower risk of subsequent hip fracture, compared to untreated controls [26]. The association between antiosteoporosis medication (AOM) and the risk of subsequent fracture after a hip fracture was investigated in another large Taiwanese cohort [27▪]. Delayed AOM initiation, starting more than 252 days after hip fracture, was associated with higher risk fracture, compared to early AOM initiation, demonstrating the importance of early AOM administration. Although a fracture risk-based strategy is recommended for initiation of osteoporosis therapy, an analysis of a large 20-year retrospective cohort study from Canada found that a in a multivariable model, a T-score $\leq$ -2.5 on a first BMD test was the dominant predictor of patients being on osteoporosis treatment, whereas a FRAX score >20% was associated with *lower* odds ratio of therapy [28].

Automated detection, using already available imaging to identify patients at risk could be successful approach, in addition to FLSs, to identify patients eligible for AOM. A novel method, based on deep learning, using lumbar spine x-rays, was able to predict osteopenia and osteoporosis with moderate accuracy, and could potentially have a role in patient identification in the future [29]. Opportunistic screening using chest computed tomography, in 414 consecutive breast cancer patients, who underwent both DXA and computed tomography, was recently tested. A moderate correlation between L1 attenuation and DXA T-score was observed, and women with attenuation values 90 HU or lower had higher fracture risk [30]. Screening using vertebral fracture assessment (VFA) to identify vertebral fractures in SUPERB-cohort of 3028 women in Sweden, was able to identify additional women at high fracture risk. Those with grade 1 vertebral fractures had increased risk of any fracture and MOF, by 67% and 86%, respectively [31▪].

## NEW STUDIES ON OSTEOPOROSIS TREATMENT AND FRACTURE PREVENTION

Exercise and targeted falls prevention have been proposed as important measures to prevent fractures. In a recent large, three-group, cluster randomized controlled trial (RCT), of men and women from general practices in England, participants were assigned to advice by mail alone, multifactorial fall prevention, or targeted exercise for those at increased risk of falls (Table 3). Over 18 months, neither the multifactorial fall prevention nor exercise reduced fracture rates [32▪▪]. In another large cluster RCT, the effect on individualized multifactorial interventions on the rate of serious fall injury in older adults (mean age 80 years, 62% women) was investigated [33▪▪]. The intervention did not result in a significantly lower rate of first adjudicated serious fall injury, providing additional, yet disappointing results, arguing against prioritizing these types of interventions. In contrast, dietary supplements consisting of additional intake of milk, yoghurt, and cheese, reduced the risk by 33% for all fractures, by 46% for hip fractures, and by 11% for falls in institutionalized older adults in large 2-year cluster RCT in Australia [34▪▪]. Study findings support that dairy food supplements are effective and should be used in aged care facilities to reduce the rates of fractures and falls.

Safety and potential cardiovascular effects of bisphosphonate therapy have been the focus of intense debate. In a prescription register-based cohort study, the associations between oral bisphosphonate (oBP) therapy and cardiovascular outcomes were investigated [35]. Patients receiving oBPs had 32% lower risk of cardiovascular events than the controls, indicating a cardio-protective role of oBP. Results from another cohort study indicated that the effect of zoledronic acid and oBP on cardiovascular outcomes could differ [36▪]. Patients who used zoledronic acid had higher risk of heart failure and all-cause mortality than patients receiving oBP. Compared to matched untreated controls, the risk of arrythmias and heart failure was higher, but the risk of cardiovascular mortality was lower in zoledronic acid-treated patients. However, due to the inherent limitations of observational studies, it could not be determined if these differences were due to selection bias or treatment effects, with zoledronic acid likely preferred by prescribers in the most fragile subset of patients where correct administration of oBPs can be a challenge.

Denosumab discontinuation results in rapid bone loss, but the importance of upholding compliance with denosumab is less clear and was recently investigated in a cohort of 151 denosumab

**Table 3.** Intervention studies

| Treatment | Study | Population | Key findings |
|---|---|---|---|
| Falls prevention and exercise. | Lamb *et al.* (2020) [32▪▪] | 9803 men and women, 70 years of age or older from 63 general practices in England. | Compared to advice by mail, targeted intervention with exercise (hazard ratio 1.20 (95% confidence interval) 0.91–1.59)) or multifactorial fall prevention (hazard ratio 1.30 (0.99–1.71)) was not effective in reducing fracture rates. |
| Multifactorial prevention of injurious falls. | Bhasin *et al.* (2020) [33▪▪] | Men and women, 70 years or older, who were at increased risk for fall injuries. 2802 participants in the intervention group and 2649 in the control group. | The rate of a first adjudicated serious fall injury was not significantly different between the groups, in a time-to-first-event analysis (4.9 events per 100 person-years in the intervention group and 5.3 in the control group; hazard ratio 0.92 (95% confidence interval) 0.80–1.06). |
| Delayed denosumab injections. | Lyu *et al.*(2020) [37] | 151 patients (95% women), on average 69 years old, who had used at least 2 denosumab injections (60mg). | Patients with a dosing interval $\leq$7 months had an annualized lumbar spine BMD increase of 3.9%, compared with patients with moderate (3.0%) or poor compliance (1.4%, P for trend 0.002). |
| Cardiovascular and skeletal safety of zoledronic acid. | Rubin *et al.* (2020) [36▪] | Matched cohorts of Danish and Swedish adults, treated with zoledronic acid (ZA; $n=8739$ in cohort 1, 8731 in cohort 2) or oral bisphosphonates (oBP; $n=25\,577$) and controls ($n=25\,924$). | Compared to oBP, ZA users had higher risk of heart failure (adjusted hazard ratio (95% confidence interval) 1.17 (1.04–1.32)) and all-cause mortality (hazard ratio 1.24 (1.15–1.34), but no increased risk in cardiovascular mortality. ZA users had lower risk of cardiovascular mortality than controls (hazard ratio 0.87 (0.77–0.98). |
| Oral bisphosphonates and cardiovascular events. | Rodríguez *et al.* (2020) [35] | Patients identified through a Danish register and one hospital. 2565 oral bisphosphonate (oBP) users (82.6% women) and 4568 (82.3% women) propensity score-matched controls. | There were 406 (15.8%) cardiovascular events in the oBP users (event rate 73.48 [66.67–80.98]); and 837 (18.3%) events in controls (104.73 [97.87–112.07]) corresponding to an adjusted hazard ratio of 0.68 (95% confidence interval) 0.60–0.77). Adjustment for BMD did not attenuate the association (hazard ratio 0.67 (0.58–0.78)). |
| Dietary calcium, protein, falls, and hip fracture. | Iuliano *et al.* (2021) [34▪▪] | Two-year cluster randomized trial including 7195 residents and age care facilities in Australia. | The effect of additional intake of milk, yoghurt and cheese vs. unchanged diet was compared. There were 324 fractures (135 hip fractures), 4302 falls, and 1974 deaths during follow-up. The intervention was associated with risk reductions of 33% for all fractures (121 vs. 203; hazard ratio 0.67 (95% confidence interval) 0.48–0.93), 46% for hip fractures (42 vs. 93; hazard ratio 0.54, 0.35- 0.83), and 11% for falls (1879 vs. 2423; hazard ratio 0.89, 0.78–0.98) |

users. Annualized BMD increments were greater in patients who had a dosing interval 7 months or shorter, compared to those with over 7 months indicating suboptimal adherence [37].

## CONCLUSION

Recent cohort studies in osteoporosis have further highlighted the importance of timely identification and treatment of people who are at high risk of suffering osteoporotic fractures. Physical performance is a strong indicator of fracture risk and one that is tightly linked to a number of chronic conditions and treatments as reviewed above and as listed in the tables. The importance of diet modification in the prevention of falls and fractures remains poorly understood after decades of research but may well offer a cost-effective way of reducing the societal fracture burden by delivering a small risk reduction to a very large number of persons. Dietary acid load may have been dismissed by many as more fad than fact, and could indeed be due to collinearity with other lifestyle factors in the absence of persuasive intervention studies, but it is a topic well worthy of investigation. Active case finding high risk patients among patients with chronic glucocorticoid exposure, Parkinson's, cerebrovascular disease, and inflammatory conditions is an attractive prospect but not one that has been tested or implemented to any great extent. From a technological point of view, advances in imaging spanning from opportunistic identification of low BMD and vertebral fractures to dedicated bone structure assessment by HR-pqCT should be able to help us

narrow the treatment gap and particularly so in the highest risk subset of patients. Further, as the cost of DNA testing plummets, targeting of osteoporosis assessment by polygenic risk scores - perhaps combined with medication history from electronic medical records - could help streamline services and capture high risk persons who are currently only identified once they have suffered one or more fractures.


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