Review

Adding to complexity: comorbidity in paediatric rheumatic disease

Eve M. D. Smith1, Helen E. Foster1,2 and Michael W. Beresford3,4

Abstract

Novel therapies including biologic agents offer paediatric rheumatologists significant opportunity to improve long-term prognosis for children with rheumatic disease. However, comorbidities related to the diseases themselves and their treatments pose specific challenges to be overcome. Prompt recognition and appropriate management will improve quality of life, effectiveness of treatment and overall prognosis. In this review, we discuss key areas of comorbidity frequently encountered in paediatric rheumatology including cardiovascular, renal, genito-urinary and visual comorbidity, bone health, drug-related issues and the influence of rheumatic disease on growth and puberty.

Key words: paediatric rheumatic disease, comorbidity, disease outcomes, medication safety, transition.

Introduction

The care of children and young people with severe, often rare, multi-system autoimmune rheumatic diseases poses a significant challenge to multi-disciplinary specialist teams (MDSTs) endeavouring to provide holistic care to patients and their families. This is compounded by a striking paucity of a rigorous evidence base for their management [1]. Childhood and adolescence is a time of profound biological development and psychological change—all of which confer additional impact on chronic, complex inflammatory conditions. Many drugs used to treat these disorders have major potential short-, medium- and long-term side effects that many young people and their parents find intolerable [2]. Compounding the complexity in managing paediatric rheumatic disorders are the frequent occurrence of single or multiple comorbidities. These can impact significantly on the disease process itself, treatment choices and contribute to the full impact of the problems to be faced by patients and their families.

Co-morbid conditions may be directly linked to the underlying disease process itself and/or treatments, or may occur independently. Increased recognition and efforts to appropriately manage comorbidities is driven by greater expectation of outcome, the significant potential impact that they can have on quality of life (QOL) and the improved prognosis of the primary disease. Diverse comorbid conditions influence outcomes differently; pulmonary and cardiac comorbidities may increase mortality; whereas localized growth abnormalities such as micrognathia may associate with low mood and depression. As many outcome studies in paediatric rheumatology predate the current approaches to treatment, it is not easy to extrapolate the relevance of these data to patients presenting currently [3, 4]. Such studies can also be difficult to compare due to differences in the terminology used internationally in these studies (e.g. JIA, JRA, JCA). Notwithstanding these challenges, we discuss key areas of comorbidity frequently encountered in paediatric rheumatology, including cardiovascular, renal and visual comorbidity, bone health and the influence of rheumatic disorders and treatment on growth and puberty.

Cardiovascular comorbidity in paediatric rheumatic disease

Atherosclerosis is a chronic inflammatory condition itself influenced by rheumatic disease-related factors such as immune complex formation, complement activation, aPLs, inflammation, corticosteroid (CS) use and endothelial dysfunction [5–8]. Significantly increased mortality from cardiovascular disease reported in adults with rheumatic disease is likely to be due in part to a clinically silent atherosclerotic process beginning during childhood.
In JIA, atherosclerotic lesions have been demonstrated in post-mortem specimens of children [9].

Carotid intima–media thickness (CIMT) has been validated against pathological studies to assess pre-clinical atherosclerotic plaques in adults [10]. CIMT has been shown to be increased in studies of patients with systemic-onset JIA, JSLE and adults with a history of JDM, compared with controls [6, 7, 11–13]. Phase contrast MRI demonstrates aortic compliance and distensibility is reduced in JIA, indicating endothelial dysfunction and subclinical atherosclerosis [6]. Doppler US of the brachial artery measuring flow-mediated dilatation is impaired in children with JIA and adults with JDM as compared with controls [5, 12]. Novel methods of screening premature atherosclerosis in young people such as static/dynamic nailfold videocapillaroscopy have been proposed [9].

The prevalence of traditional cardiovascular risk factors (hypertension, BMI, hyperlipidaemia, impaired glucose tolerance, reduced aerobic fitness), are observed in children with rheumatic diseases [14–16]. Studies of lipid metabolism in children with JSLE demonstrate that dyslipoproteinaemia appears inherent to the disease process with depressed high density lipoprotein (HDL), and elevated very low density lipoprotein (VLDL) cholesterol and triglycerides [11]. Lipid abnormalities occur early in the JSLE disease course (within the first 4 years) [14]. Treatment with CSs has been shown to exacerbate dyslipoproteinaemia, increasing total cholesterol, VLDL cholesterol and triglycerides [15]. Conversely however, treatment with CSs has also been shown to negatively correlate with atherosclerotic plaque formation in adult patients with SLE, supporting the notion that aggressive immunosuppressive therapy may lower the likelihood of atherosclerotic plaque formation [17]. In adults with SLE, hyperhomocysteinaemia has also been implicated in the pathogenesis of coronary artery disease and linked to thromboembolic events. Studies in JSLE have reported raised homocysteine levels although further prospective, long-term studies are required to further elucidate its role as a cardiovascular risk factor in children [18, 19].

Studies of atherosclerosis prevention in paediatric rheumatic disease are lacking. As children and young people with rheumatic disease increasingly have less physical and functional disability, MDSTs should provide advice and encouragement in paediatric rheumatology clinics to facilitate lifestyle changes that reduce obesity and atherosclerosis risk and improve fitness. Use of HCQ has been associated with reductions in cholesterol and apolipoprotein B levels in JSLE, and lower cholesterol, low density lipoprotein (LDL) levels and vascular event frequency in adult SLE [20–22]. Statin use is reported as being associated with a variety of inflammatory myopathies, and is consequently usually avoided in such conditions [23].

In JSLE, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial [13] randomized patients to either atorvastatin or placebo and assessed whether 3 years of treatment was effective in reducing atherosclerosis progression as measured by CIMT. Atorvastatin did not have a statistically significant effect on mean CIMT progression; however, CIMT progression rates were significantly higher in the placebo group than those previously reported for the general paediatric population and children with familial hypercholesterolaemia. This supports the view that JSLE patients are at increased risk of atherosclerosis. Cholesterol and LDL levels also decreased significantly from baseline in the treatment group. Importantly, the adverse events rate was comparable between treatment and placebo groups over the 3-year treatment period [13]. This trial, the first randomized controlled trial of its kind in paediatric rheumatic disorders, exemplifies some significant challenges inherent to paediatric research that compounds the challenges of addressing additional issues related to comorbidities such as cardiovascular risk (Table 1).

Renal and genito-urinary comorbidity in paediatric rheumatic disease

Comorbidity due to renal disease is more prevalent and generally more severe in JSLE as compared with adult-onset lupus, with up to 80% of JSLE patients having renal disease at some point in their disease course [25]. Studies looking at the pattern of damage accrual between 1 and 5 years after JSLE onset have found renal damage to be one of the most commonly encountered complications, occurring in between 1.8 and 12.1% of patients during the time studied using the Systemic Lupus International Collaboration Clinic (SLICC)/ACR damage index (ACR SDI) measurements [25, 26]. Table 2 summarizes the data on SLICC/ACR damage index reported organ damage in two JSLE populations.

There is significant concern that some irreversible renal damage may occur before the onset of clinically detectable disease [27]. Up to 20% of children with proliferative LN develop renal failure over a 10-year period [28]. Potential biomarkers of early LN disease, disease flares and predictors of disease remission are increasingly being studied and a number have been identified [29] and include: urinary monocyte chemoattractant protein-1 (MCP1), alpha-1-acid glycoprotein (AGP) [30], serum CXC motif ligand 13 (CXCL 13) [31], B-cell activating factor, regulated upon activation normal T-cell expressed and secreted (RANTES), soluble vascular adhesion molecule 1 (sVCAM-1), urinary neutrophil gelatinase-associated lipocalin (uNGAL) [32, 33] and complement fragments Bb, C3d-CIC and C5. Complement fragment C1q is reduced in LN [34]. The optimal biomarker or combination of parameters requires further longitudinal analysis to determine which are best at predicting LN flares and outcome.

Historically renal amyloidosis was a major complication of JIA and other paediatric CTDs, now significantly reduced through use of intensive immunosuppressive treatment regimens [34]. ANCA-associated GN can occur, albeit rarely in systemic-onset JIA and focal segmental GN/mild mesangial GN have been reported in children with polyarticular JIA [35, 36].
Bone health in paediatric rheumatic disease

Decreased BMC and BMD along with increased fracture risk can occur in children with rheumatic diseases, resulting in considerable pain and comorbidity [37–42]. Peak bone mass is reached at the end of adolescence and is an important determinant of osteoporosis and future fracture risk. Multiple factors may contribute to osteopenia, including inflammation, CS use, diseases activity, nutrition, physical inactivity, limited exposure to sunlight and delays in pubertal development, all potentially important in a young person with a rheumatic disorder [37, 38, 42–46]. Even in the absence of CS treatment, 30% of post-pubertal female patients with mild-to-moderate JIA have low total body BMC [42]. Similarly, young adults with JIA can have abnormal BMD, despite achieving full disease remission [47, 48]. Further studies that explore potential factors contributing to low BMC/BMD are highlighted in Table 3.

### Table 1 Challenges in paediatric research illustrated by examples from the APPLE trial

<table>
<thead>
<tr>
<th>Paediatric research challenges</th>
<th>Example from APPLE trial and discussion of the factors contributing to these challenges</th>
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<tr>
<td>Drug compliance</td>
<td>Example: Adherence rate of 62% [13] Contributing factors/discussion: Study carried out over 3 years. Adherence often problematic in multi-year trials but may be particularly low in adolescents who view preventative health care measures as low on their list of priorities. Patients in early adulthood are a particularly mobile population due to changes in education, work and the need to transition to adult rheumatology services. Consequently, a proactive approach to follow-up and retention is required, creating close links with adult rheumatology colleagues.</td>
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<td>Patient retention in studies involving young people</td>
<td>Example: 17% drop-out rate [13] Contributing factors/discussion: Contributing factors are similar to those affecting drug compliance. It is increasingly recognized that extra strategies are required to optimize retention of young people. This may include provision of reminders (phone call, text, e-mail) or use of more innovative methods of contacting patients, e.g. web-based interventions, chat rooms, social networking sites.</td>
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<td>Study drug dosage</td>
<td>Example: Patients received either 10-20 mg/day atorvastatin depending on weight [13]. In the adult Lupus Atherosclerosis Prevention study (LAPS), patients were given 40 mg of atorvastatin daily. APPLE trial patients weighing &gt;50 kg (adult size) received half the dose of LAPS patients [24]. Contributing factors/discussion: Research in children frequently follows from adult studies. Investigators are faced with inferring an appropriate drug dose, and may be conservative in children due to safety concerns. This may affect the ability of the medication to have a measurable effect.</td>
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<td>Defining a significant primary end-point in the paediatric context</td>
<td>Example: A clinically significant change in the mean CIMT was defined as a 0.0045 mm/year difference in the progression rates between the atorvastatin and placebo groups [13]. Contributing factors/discussion: The threshold for a clinically significant increase in CIMT was based on adult epidemiological studies and extrapolated for use in the APPLE trial, which included children and adolescents of 10–21 years of age. Lack of standardized measurements in paediatrics may have affected interpretation of the results.</td>
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<td>Rigorous exclusion criteria</td>
<td>Example: Due to safety concerns, many patients with the highest risk of atherosclerotic disease were excluded (e.g. patients with severe hypercholesterolaemia, renal insufficiency or active nephrotic syndrome) [13]. Contributing factors: Stringent exclusion criteria are necessary to maintain optimal safety but affect the generalizability of study results. The exclusion criteria also led to under-representation of African-American patients, as they tend to have greater disease severity, also affecting the generalizability of study results.</td>
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Studies investigating biochemical markers of bone turnover in JIA demonstrate increased bone reabsorption over bone formation, although some studies show a reduction in bone formation only [39, 42, 49]. Abnormalities in bone turnover are associated with increased disease activity, joint destruction, longer disease duration and pro-inflammatory cytokines [50, 51]. Anti-TNF treatment in MTX-refractory polyarticular JIA patients is associated with significant improvements in lumbar spine BMD z-score and BMC [52].

A negative correlation between bone mass and cumulative glucocorticoid dose occurs in children with a variety of underlying diseases treated with glucocorticoids [53]. During childhood and adolescence, glucocorticoid treatment impairs bone mass accumulation, leading to a lower peak bone mass. High dose MTX in cancer treatment is associated with osteopenia but does not negatively influence bone mass at the doses used in paediatric rheumatic diseases [54].

Bisphosphonates are an effective treatment for osteoporosis in adults, with studies showing improvements in BMD and a reduction in fracture risk. Much less is known about their use in children. A recent review looking at the effectiveness of bisphosphonates in JIA patients with fragility fractures found treatment to increase mean spinal BMD by 4.5–19.1% [55]. Further studies are required to clarify whether these positive effects continue over time, the length of treatment required, the maximal bone mass that can occur and the long-term effect on fracture risk. Small studies looking at calcium, vitamin D and calcitonin have shown such supplementation to have a beneficial effect on bone mass. There have not been any controlled studies exploring whether these treatments should be given on a preventative basis or whether they should be reserved for when the BMD is below a certain threshold [39].

Physical activity is a major non-pharmacological method for increasing and maintaining peak BMD and strength. Adults who participate in high impact sports and exercises have a higher BMD [56]. Studies in healthy children have supported the efficacy of weight bearing exercises in increasing BMD [57]. Studies addressing the amount, duration and frequency of weight bearing exercise, along with safety and efficacy of such exercise regimens in paediatric rheumatic disease are necessary. Alcohol intake and smoking are associated with osteoporosis and increased fracture risk and should be discussed with adolescent patients [58].

**Ophthalmological complications of paediatric rheumatic disease**

Uveitis occurs in 12–38% of JIA patients [59–61], often asymptptomatically. The presence of uveitis may precede the development of arthritis, and often flares of uveitis and arthritis do not coincide [62] emphasizing the need for eye screening [63]. Severe JIA-associated uveitis is associated with cataracts, increased intra-ocular pressure, band keratopathy and posterior synechiae in up to 75% of cases [62, 64, 65]. The risk of developing uveitis varies according to the subtype of JIA with patients with oligoarticular disease who are ANA-positive having the highest frequency of uveitis, followed by polyarticular and systemic-onset subtypes [62, 64]. Other risk factors include: female gender, <6 years old at diagnosis and having JIA for <4 years [66]. Uveitis-associated complications are
<table>
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<tr>
<th>Study and patients</th>
<th>Potential contributing factors assessed</th>
<th>BMC/BMD of patients studied</th>
<th>Factors found to be associated with BMC/BMD</th>
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<tr>
<td>Lien et al. [38], n = 105 JIA patients</td>
<td>Sex, age, weight, height, BMI, physical activity levels, lean mass, Tanner stage, JIA subtype, Daily calcium and vitamin D intake, CS use, Disease activity, Joint examination, Radiographic changes</td>
<td>41% of patients had low BMC, 34% had total low BMD</td>
<td>Duration of active disease, Number of joints with restricted mobility, Bone area, Urinary deoxypyridinoline, Age at diagnosis, Low weight and height</td>
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<td>Henderson et al. [42], n = 36 JIA (steroid naive); 51 healthy control patients</td>
<td>Anthropometric measurements, Laboratory measures of bone metabolism, Disease activity, Diet, Physical activity</td>
<td>Total BMC was 4.5% lower in JIA patients than in controls</td>
<td>Lean body mass—showed a protective effect on total body BMC with a 0.56 risk reduction for low total body BMC</td>
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<td>Alsufyani et al. [43], n = 25 JSLE; seven JDM; four systemic vasculitis patients</td>
<td>Sex, Ethnicity, Disease duration, Cumulative steroid dose, Mean daily CS dose, Daily calcium intake, Physical activity level</td>
<td>Low BMD z-score in: 40% of JSLE patients and 27% of JDM + vasculitis patients</td>
<td>Patients with a lower BMD were: Younger, Pre-puberal, On a higher CS dose, When compared with children with a normal BMD</td>
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<td>Kashef et al. [46], n = 13 JSLE; five JIA; 20 healthy control patients</td>
<td>Height, weight, age, Cumulative steroid dose, Daily steroid dose, Disease activity, Disease duration</td>
<td>BMD was significantly lower in patients compared with controls</td>
<td>No factors independently correlated with low BMD</td>
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<tr>
<td>Compeyrot-Lacassagne et al. [37], 64 JSLE patients</td>
<td>Sex, ethnicity, BMI, Age at diagnosis, Pubertal status, Age at DEXA scan, QOL, Clinical features, Disease activity and damage, Medication use/duration</td>
<td>Low spine BMD in 37% of patients, 20.3% to a osteoporotic level, Low hip BMD in 18.8%</td>
<td>Low BMD associated with: Disease duration, Duration of CS use, Cumulative steroid dose, Disease duration was the only independent predictor of low BMD</td>
</tr>
<tr>
<td>Castrol et al. [44], n = 16 JSLE; 32 control patients</td>
<td>Weight, height, Tanner stage, Disease duration, Mean daily steroid dose, Cumulative steroid dose, Disease activity,</td>
<td>Difference in BMD of JSLE patients and controls not statistically significant</td>
<td>No factors associated with reduced BMD</td>
</tr>
<tr>
<td>Stewart et al. [45], n = 15 JDM patients (10 active + five with inactive disease)</td>
<td>Demographics, Disease activity, Steroid treatment</td>
<td>Abnormal BMD in 60% with active disease and 80% with inactive disease</td>
<td>Disease activity, Steroid treatment</td>
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DEXA: Dual-emission X-ray absorptiometry.
TABLE 4 Visual outcomes in JIA-associated uveitis

<table>
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<tr>
<th>Complication</th>
<th>Reported complication rates</th>
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<tr>
<td>Cataract</td>
<td>In a longitudinal study of 55 patients with uveitis, cataract was present in 42 and 51%, 7 and 24 years after a diagnosis of uveitis, respectively [64].</td>
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<tr>
<td>Glaucoma</td>
<td>Uveitis-associated glaucoma present in 5 and 22%, 7 and 24 years after a diagnosis of uveitis, respectively [64].</td>
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<td>Impaired visual acuity</td>
<td>A case series of 142 patients with uveitis identified good visual acuity in 90.8% of all eyes, impaired visual acuity in 3.4% and blindness in 5.7%. Only two patients had reduced visual acuity in both eyes [65]. Retrospective case series of JIA-associated uveitis—36% of affected eyes had 20/50 or worse and 24% had 20/200 or worse visual acuity at presentation [68]. In a retrospective review—male gender associated with a 6.6-fold increased odds of blindness [69].</td>
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more likely in those who develop chronic uveitis, psoriatic JIA, a diagnosis of uveitis before or at the time of arthritis onset or in patients who are symptomatic at the time of uveitis onset [67]. Visual outcomes and rates of complications in JIA-associated uveitis are summarized in Table 4.

Topical CSs are first-line treatment of JIA-associated uveitis although complications include: increased intracocular pressure and cataract formation. Systemic CSs and peri-ocular steroid injections may be required in refractory cases. Increasingly systemic immunosuppressive agents are used to reduce the risks of sight threatening complications and achieve a steroid sparing effect. MTX is well established as the first-line disease-modifying agent in JIA; however, 15–50% of children will have refractory uveitis despite optimal treatment with MTX [70]. Anti-TNF agents vary in their efficacy in severe refractory uveitis [71], and reports of new-onset uveitis-associated with etanercept use in JIA [72] has lead to the preferential use of infliximab or adalimumab in JIA patients with uveitis. When treatment with one subtype of anti-TNF has been ineffective switching to another anti-TNF agent can be successful in achieving control of intra-ocular inflammation [70]. Trials of anti-TNF therapy in JIA-associated uveitis are currently underway (https://www.clinicaltrialsregister.eu/).

Growth in paediatric rheumatic disease

Growth disorders are common in children with chronic rheumatic diseases and have been attributed to a range of contributing factors including disease duration and severity, age at diseases onset, immobility, suboptimal nutrition and CS therapy. In JIA, the prevalence of significant short stature (final height z-score defined as less than twice the s.d. score adjusted for age) ranges from 11% of all JIA subtypes, to 41% of patients with systemic-onset disease [3, 73, 74]. JSLE patients show a significant reduction in parent-adjusted height z-scores, with males being most affected [75]. The children most at risk of having a height deficit were those that presented in the pre-pubertal/peri-pubertal period, who were treated with >400 mg/kg cumulative dose of CSs. Further, follow-up studies exploring the effects of biologics, steroid-sparing regimens and improved disease control on growth are warranted.

Growth hormone (GH) and insulin-like growth factor (IGF-1) are the most important regulators of growth out with the neonatal period. In children with JIA and significant growth impairment, low levels of IGF-1 are described with normal ongoing pulsatile GH secretion [39, 76]. Table 5 describes the relationship between the inflammatory cytokines implicated in rheumatic disease and hormonal regulators of growth. JIA patients treated with GH for 1 year can achieve a significant increase in height velocity [78]. In children with systemic and polyarticular JIA, GH therapy improves height velocity but not necessarily the predicted target height (final height z-score — 1.6 in treated patients and — 3.4 in controls) [79]. GH therapy for children with severe JIA receiving 12–15 months of steroid treatment can normalize height velocity during the first year of treatment, remaining normal over the subsequent 2 years [80]. These studies suggest that GH improves short-term height velocity but may not entirely reverse the effects of treatment and underlying disease on growth. Studies of GH safety in JIA have involved small numbers of patients over short periods of follow-up, but overall suggest a satisfactory safety profile. Initial concerns of combined GH and CS therapy leading to impaired glucose tolerance have been unsupported by clinical trials but there have, however, been a few reports of GH associated flares in arthritis. The decision to treat with GH should therefore be made cautiously [81].

The pattern of growth disturbance in JIA can be generalized or localized and tends to vary according to the subtype. More severe JIA is associated with generalized growth impairment. Oligoarticular JIA typically can be associated with increased growth in the affected limb in young children and decrease growth due to premature fusion of the epiphyses in older children [76, 77] resulting in limb or digit length discrepancy or micrognathia. In practice, growth retardation, especially localized, is felt to be becoming less common with current treatment approaches and often is a feature of delay in access to specialist care. Growth can be reversibly impaired during periods of intensive steroid therapy [82] although full catch-up growth is not always attained following cessation of steroid treatment [83].
TABLE 5 Influence of inflammatory cytokines on hormonal regulators of growth and local cellular structures

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<tr>
<th>Cytokine</th>
<th>Effect on growth</th>
<th>Mechanism</th>
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<tr>
<td>IL-1β</td>
<td>General growth retardation</td>
<td>Accelerates degradation of IGF-1 and leads to the development of phosphorylated IGF-binding protein (IGFBP1), which prevents IGF binding to its receptor [39, 75]</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Local growth abnormalities</td>
<td>Affects growth plate chondrocyte dynamics and increases longitudinal bone growth [39, 76, 77]</td>
</tr>
<tr>
<td>IL-6</td>
<td>Systemic effect on growth retardation</td>
<td>Accelerates degradation of IGF-1 [39] Alters growth hormone secretion [76]</td>
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The impact of anti-TNF treatment on growth velocity has been studied in polyarticular JIA patients. Those with delayed growth before anti-TNF treatment displayed a significant increase in growth velocity at 2 years after commencing treatment [84]. When glucocorticoid dosage was corrected for, the change in inflammatory activity emerged as a significant predictor of growth velocity, suggesting that reduced inflammation affected growth velocity rather than the anti-TNF treatment having a direct effect on growth. Comparing growth velocity in new polyarticular JIA patients treated with MTX alone, and patients who had etanercept added to MTX treatment due to inadequate disease control, indicates growth velocity only increases significantly in the group receiving etanercept [52]. Similarly, looking at polyarticular and systemic-onset JIA patients treated with etanercept, etanercept and MTX or MTX alone for 3 years, statistically significant increases in mean height were only seen in those who received etanercept, with or without MTX [85].

Puberty in paediatric rheumatic disease

Pubertal delay has been reported widely in adolescents with paediatric-onset rheumatic diseases. In JSLE, pubertal onset may be delayed in as many as 15 and 24% of the female and male JSLE patients, respectively [76]. In a Brazilian study involving 30 patients with JSLE and 30 matched controls, mean menarchal age was 13.1 years in lupus patients vs 11.6 years in controls [86]. A high prevalence of menstrual disturbance is reported in JSLE, varying from irregular menses, long cycle lengths to postmenarche amenorrhea [75, 86]; although these symptoms may cause concern among young female patients, there is no evidence of long-term impact on fertility in later life. The hormone profiles of adolescent females with JSLE differ from healthy controls, with increased median follicle stimulating hormone levels and lower median progesterone levels [86]. In JIA, age-of-onset of menarche has been compared between patients and their mothers, revealing the timing of menarche to also be later in JIA and particularly delayed in patients who had systemic/polyarticular JIA or received glucocorticoids [87]. Pubertal delay can have significant effect on self-esteem and relationships with peers, and especially when associated with a delayed growth spurt; this can result in the perception of adolescents appearing younger than they actually are and being treated in a way that is inappropriate to their emotional developmental stage.

QOL

Chronic illnesses can lead to significant physical and psychosocial comorbidity. Paediatric rheumatologists have increasingly become aware of the need to measure health-related QOL (HRQOL). A number of assessments can be used to do this, including the Child Health Questionnaire (CHQ) and Paediatric Quality of Life Inventory (PedsQL) [88, 89]. Three international studies have assessed HRQOL and its determinants in JIA, JSLE and JDM [80, 90, 91]. In all three studies, significant impairment of HRQOL was identified in the physical domains of the CHQ. Physical well-being was correlated with the degree of functional impairment [90–92], whereas pain had the greatest influence on psychosocial health [90]. Patients with persistent oligoarthritis had better HRQOL compared with other subtypes of JIA, whereas patients with systemic arthritis, polyarthritis and extended oligoarthritis had similar HRQOL [90]. In JSLE, the SLEDAI score was significantly correlated with the physical and psychosocial summary scores of the CHQ. The SLICC/ACR SDI score was also significantly correlated with the physical summary score, suggesting that HRQOL in JSLE may be affected by disease activity and accumulated damage [91]. In JDM, poorer physical and psychosocial summary scores were associated with increasing levels of disease activity and reduced muscle strength [92].

QOL assessment in adults with all types of JIA indicates a profound effect on generic health status and QOL at a median age of 30 years. Despite excellent educational attainment, a high rate of unemployment among these patients can exist [93, 94]. The challenge with modern therapies and transitional care programmes is to improve outcomes relevant to patient priorities—being employed has considerable impact on well being and QOL but the impact in adult cohorts may not be fully evident until years to come, when these patients reach their third and fourth decade.
Drug-related comorbidity

Many medications used in paediatric rheumatology can have potential side effects. CSs clearly have the potential for many adverse events, which have largely been detailed above. NSAIDs can be associated with acute kidney injury, hypertension and interstitial nephritis in children. A prospective study evaluating renal complications in JIA patients treated for 6 months vs. NSAIDs found 22 (10%) of the 226 children had microscopic haematuria and/or proteinuria in 1 urinalysis. No patients developed hypertension and in 21 of the 22 patients the abnormalities resolved spontaneously [95].

MTX is one of the most useful and commonly used drugs in paediatric rheumatology due to its efficacy and the availability of long-term safety data. Intolerance to MTX, namely nausea and vomiting, stomach ache, sore mouth and behavioural symptoms may occur in up to 44% of JIA patients receiving oral MTX and 67% receiving parenteral treatment [96]. Symptoms can occur after taking MTX, before (anticipatory) and when thinking of MTX (associative). Newer biologic treatments have transformed the management of JIA patients with MTX intolerance and MTX-resistant disease. However, with an increasing number of clinical trials and the consistent availability of these agents only within recent years, longer term safety data are not available, and their long-term use as first-line agents remain cautionary.

In 2009, the US Food and Drugs Administration (FDA) issued a warning related to the potential development of malignancies in patients with JIA who had used anti-TNF medications for 2.5 years. This was based on a study that included 248 children with both JIA and inflammatory bowel disease who developed cancer while receiving anti-TNF therapy and other immunosuppressive agents. These findings clearly cannot be ignored, but recent data suggest that JIA per se and not the exposure to MTX or biologics may be associated with an increased risk of malignancy [97]. In RA, evidence has accumulated that disease activity itself is associated with risk of lymphoma [98]. Observational studies exploring the link between anti-TNF treatment and cancer risk have not indicated any increased risk of cancer, although the follow-up periods have been rather short (mean follow-up of 3 years) [99].

The long-term safety (and efficacy) of biologics in paediatric rheumatic disorders has become a key priority of both national and international collaborative efforts. Biologics Registries in the UK, Germany, Holland and a number of other European countries, along with similar North American initiatives have been collecting information on long-term safety and effectiveness of biologic agents in children with rheumatic diseases since 2000. Longer term follow-up and collaborative collation of data internationally is necessary to improve reliability of these observations and fully address the concerns regarding paediatric rheumatic disease, biologic treatment and malignancy and forms the basis of the international PharmaChild study (http://clinicaltrials.gov/ct2/show/NCT01399281).

CYC is used to treat severe manifestations of JSLE, JDM and vasculitis. Bladder toxicity, cancer and haemorrhagic cystitis are seen in oncology patients where prolonged courses of oral CYC are used. In autoimmune rheumatic diseases where intermittent i.v. CYC is used such complications are rarely seen. Lowering the cumulative dose, concomitant use of MESNA, i.v. therapy and adequate hydration are all important in minimizing risks [100]. Increased risk of cervical dysplasia is associated with CYC use in SLE. It is important that young women with lupus follow established guidelines for cervical cancer screening and human papilloma virus vaccination [101, 102].

Mortality associated with paediatric rheumatic disease

Studies looking at mortality in paediatric rheumatic disease are largely unable to determine the influence of comorbid disease on mortality due to the lack of adequate longitudinal follow-up. Adults with a history of JIA and a comorbid autoimmune disease (e.g. autoimmune hepatitis, insulin-dependent diabetes mellitus, common variable immunodeficiency, Graves’ disease) have a shorter life expectancy than age- and sex-matched members of the general population [103]. Data from the Indianapolis paediatric rheumatology registry [104] has been used to describe the standardized mortality ratio (SMR, ratio of observed deaths to expected deaths) and causes of death of a cohort of paediatric rheumatology patients (49,023 patients studied between 1993 and 2001). The SMR was increased in patients with JSLE and JDM [3.06 (95% CI 1.78, 4.90) and 2.64 (95% CI 0.86, 6.17), respectively]. For patients with all types of JRA, SMR was less than that of the cohort as a whole. Causes of death were related to the underlying rheumatic disease and its complications in 35% and treatment complications in a further 10% of patients. In this recent study, the SMR for systemic JRA, JSLE, JDM and vasculitis was significantly lower than that reported in previous studies. This may be due to improvements in medical management of rheumatic disease, but longer term follow-up studies including different cohorts of patients are required to see whether these results are reproducible or whether differing trends in mortality develop with current treatment regimens.

Transition

Transition from paediatric to adolescent to adult rheumatology services is a particularly challenging time when young people are expected to take increasing responsibility for their own health and well-being; however, the difficulties many young people face is exemplified by reduced adherence to treatment regimens, risk-taking behaviours and worse clinical outcomes. Timely discussions must be held between MDST professionals and young people to improve their awareness of long-term comorbidities that may be reduced by modifying lifestyle factors (such as healthy eating, regular exercise,
avoidance of smoking and limiting alcohol intake) as well as optimal adherence to treatment regimens.

Conclusion
The holistic care of children and young people with complex, chronic rheumatic disorders is by definition complex and challenging. Identification and management of comorbidity in paediatric rheumatic disease is increasingly becoming important with improving medical therapies and approaches to treatment. Novel therapies including biologic agents provide significant opportunity to improve QOL and long-term prognosis. By raising awareness of the importance of comorbid conditions this review aims to focus and direct paediatric and adult rheumatologists to address their current care and practice. Potential complications and comorbid conditions arising from these disorders and their treatment regimens require specific attention at an early stage, especially as clinical effects may only be apparent in the distant future.

It is therefore imperative that we consider comorbidities sooner rather than later in order to further improve long-term patient outcomes. Lifestyle issues are likely to be important and need to be addressed in generic health advice. Specific challenges to overcome the paucity of an evidence base to direct care of these comorbid conditions must be addressed to determine optimal standards of care for comorbidity prevention. This requires proactive national and international collaborative efforts of researchers across different disciplines in prospective, long-term, collaborative follow-up studies.

Rheumatology key messages
- Identification of comorbidity is increasingly important with improvements in the prognosis of underlying paediatric rheumatic diseases.
- The evidence base underpinning paediatric comorbidity management must be addressed to determine optimal standards of care.
- Long-term observational studies spanning the transition period are key to improving understanding of comorbidities in paediatric rheumatic disease.

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