Challenges in juvenile-onset spondyloarthritis

In this article, we analyze some of the challenges in the area of juvenile-onset spondyloarthritis from our own perspective. Our approach took into account some of the different meanings of ‘challenge’, and in this sense we present three big elements in relation to juvenile-onset spondyloarthritis: the challenges confronted by the patient and their family; the physicians and their teams; and the disease itself. The spectrum of challenges confronted by children, parents and physicians when facing a chronic disease are certainly wide, but it is a task for all participants in this interplay of experiences.

The term juvenile-onset spondyloarthritis (SpA) refers to a group of diseases and syndromes in which the onset of symptoms occurs before the age of 16 years and the main features are familial aggregation. HLA-B27 association, peripheral arthritis and enthesitis, as well as sacroilitis and spondylitis in some cases. This group of diseases is a counterpart to the classical description of SpA in the adult population, which currently includes ankylosing spondylitis (AS), undifferentiated SpA, psoriatic arthritis (PsA), Crohn’s disease as well as ulcerative colitis SpA and reactive arthritis (ReA). Enthesitis-related arthritis (ERA) is the name of the subgroup of juvenile idiopathic arthritis (JIA), which is equivalent to juvenile-onset SpA to some extent. The incidence of juvenile-onset SpA ranges from 2.1 per 100,000 [1] in Canadian children to 24.0 per 100,000 children in Western Canadian Indians [2]. In pediatric rheumatology clinics, the ratio between juvenile-onset SpA and other arthritis reaches 0.90:1.0 [3].

Over the last 30 years, there has been a constant increase in the knowledge of the epidemiological, pathogenic, clinical and therapeutic aspects of SpA. With the advent of better therapies, and particularly with the use of TNF-α blockers in AS and the possibility of modifying the inflammatory component of the disease, attempts to detect the disease in its earliest stage have been made. Today, we have new classification and diagnostic criteria of SpA and data on the role of HLA-B27 and MRI of the sacroiliac joints and spine as classification tests. Similarly, the concept behind SpA is moving in the same direction. Regarding juvenile-onset SpA, changes have been slower than in the adult-onset area. Despite the fact that cases of juvenile-onset SpA are today frequently recognized in the clinical setting, it seems that there is no complete agreement in their concept, classification and relationship with adult-onset SpA.

In this article we analyze the challenges that, from our personal view, exist in the area of juvenile-onset SpA (Table 1). We took advantage of the various definitions of ‘challenge’ and then approached them from three different but related perspectives: the patient and their family, the physician and their team, and the disease itself (Figure 1).

Challenges for the patient & close relatives

- Identifying early signs & symptoms of disease

Children and adolescents with juvenile-onset SpA suffer from pain, swelling and functional impairment that mostly affects the knees, ankles and joints of the feet [4]. However, the most characteristic signs are mid-foot and heel pain, and in a few cases, sacroiliac and spinal pain and reduced mobility several years after onset [5]. Thus, peripheral arthritis and enthesitis at onset and axial involvement later on are characteristic of juvenile-onset SpA (6,7). In some exceptions, patients present with a severe combination of such symptoms within 3 years of onset [8]. Generally, juvenile-onset SpA patients with insidious onset, slight or moderate intermittent symptoms in multiple joints and entheses are most frequently seen by physicians today, which is perhaps as a consequence of earlier referrals to specialized departments compared with in the past [3].

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Rubén Burgos-Vargas1,2,†, Ingris Peláez-Ballestas1,2,† & Raúl Gutiérrez-Suárez†,2

†Author for correspondence:
1Rheumatology Department, Hospital General de México, Dr Balmis 148, DF 06720, México
Tel.: +52 555 374 0943
Fax: +52 555 533 4180
burgosv@prodigy.net.mx
2Faculty of Medicine, Universidad Nacional Autónoma de México, Mexico

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Early on in the course of the disease, their recognition and differential diagnosis may represent an important problem, particularly when children present with nonspecific complaints (i.e., fatigue, tiredness, and ill-defined aches and pains). Symptoms are frequently attributed to injuries and overuse as a consequence of games and sports, and diagnoses range from ankle sprain, meniscus rupture to Legg–Calvé–Perthes and Osgood–Schlatter’s diseases. Patients with monoarticular involvement of the hips are often diagnosed as having toxic synovitis of the hip or even TB and other types of septic arthritis. These circumstances yield mistreatment in early disease and late referral to rheumatology departments. Awareness of chronic arthritis in children in the community, as well as among general practitioners, pediatricians and orthopedic surgeons, is needed to improve the recognition of juvenile-onset SpA and JIA as a whole.

**Challenges Possible strategies to overcome challenge**

<table>
<thead>
<tr>
<th>Challenges for the patient and relatives</th>
<th>Possible strategies to overcome challenge</th>
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<tbody>
<tr>
<td>To identify the earliest manifestations of the disease and to be referred to the specialist as soon as possible</td>
<td>Provide information for parents and teachers</td>
</tr>
<tr>
<td></td>
<td>Educate medical students, pediatric and rheumatology fellows, general physicians, pediatricians and rheumatologist</td>
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<tr>
<td>To confront the biologic and physical consequences of the disease; to confront the suffering associated with a chronic illness</td>
<td>Improve the communication, collaboration and support between family members</td>
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<td></td>
<td>Improve communication with the treating physician</td>
</tr>
<tr>
<td>To receive the best available treatment</td>
<td>Get information from the physician and their team, discuss the benefits and risks of each treatment, get proper funding, try to dismiss alternative therapies</td>
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**Challenges for the treating physician and their team**

<table>
<thead>
<tr>
<th>Challenges for the treating physician and their team</th>
<th>Possible strategies to overcome challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>To understand the concepts behind the names and classification criteria and differentiate this group of diseases from other arthritides in children</td>
<td>Set groups of experts to discuss and produce recommendations on the nomenclature, diagnosis and classification of this group of disorders based on the evidence and experts’ opinions</td>
</tr>
<tr>
<td>To recognize the relation between juvenile- and adult-onset forms</td>
<td>Review the literature and design cohort studies</td>
</tr>
<tr>
<td>To identify prognostic factors</td>
<td>Define outcome measures and design multinational cohort studies</td>
</tr>
<tr>
<td>To provide the best available treatment</td>
<td>Design clinical trials specific for this group of disorders and set therapeutic recommendations according to evidence and experts’ opinions</td>
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**Challenges for the disease itself**

<table>
<thead>
<tr>
<th>Challenges for the disease itself</th>
<th>Possible strategies to overcome challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>To get recognition as a group of rheumatic diseases in children</td>
<td>This is something that depends on the impact of these diseases on the patients and their relatives and the medical team</td>
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</table>

A total of 60% of the patients have moderate-to-severe functional limitations 10 years after onset, particularly those with disease activity for more than 5 years [10]; however, low-level disability has also been found after 27 years of disease [12]. Compared with other subgroups of JIA, patients with juvenile-onset SpA have higher bodily pain and childhood health assessment questionnaire scores, poorer physical health and lower physical functioning and health-related quality of life (HRQoL) [13–15]. Patients with juvenile-onset PsA had poorer health than the healthy population 15 years after onset and lower SF-36 scores than other JIA subgroups by 23 years of disease [16].

**Confronting the suffering of a chronic illness**

Qualitative investigations at our department have shown that patients with JIA, including juvenile-onset SpA, confront serious problems, far beyond those identified in the quantitative assessment of disease activity and HRQoL. [17]. Children and adolescents with juvenile-onset SpA face social, educational and economical barriers resulting in isolation, poor education, few job opportunities, and even a number of obstacles to establish and keep a new family.
being a child or an adolescent with juvenile-onset SpA in multiplex case families where older brothers have experienced the same disease for years may have contradictory effects [18]. While most patients receive orientation and help from their older siblings, some patients might be the target of negative attitudes.

Children with JIA, including juvenile-onset SpA, may be misdiagnosed and mistreated by physicians who are not aware of this type of disease [17]. In this situation, patients and their relatives start a period of variable duration consisting of diverse medical, complementary, and alternative diagnostic and therapeutic experiences, which we have termed ‘pilgrimage’. The series of experiences before diagnosis is made constitute the prediagnostic pilgrimage; the experiences that come afterwards, specifically those explaining the disease and chronicity, are known as postdiagnostic pilgrimage. Pilgrimage, conceived as the process of living chronically with JIA, is perceived by children and their relatives in different ways and their suffering stands at different levels. The decision to start and follow a new treatment, particularly TNF blockers, is a complex process that includes patients and relatives’ knowledge, beliefs, trust in others (mainly their doctor), expectative and economic support [19].

In order to approach these kind of issues it is certainly necessary to understand that ‘illness’ is the definition given by the patient themselves to their ‘unwell’ status of health and the cultural dimensions of disease, particularly the semiotic, semiological and phenomenological construction of symptoms [20–22]. ‘Suffering’ refers to the meaning of disease and its treatment according to the individual’s experiences throughout the course of the disease [20]. To approach these issues, we usually follow the explanatory models theory, which refers to the meaning and sense that each of the individuals involved in the clinical process gives to disease and treatment [21], and emphasizes the interaction between the patient and health professionals [20]. The course of juvenile-onset SpA, as well as other forms of JIA, may be approached through the trajectory of illness theory, which focuses on social and cultural events, which are usually interpreted in medical terms [23]. It does not only refer to the physiological events, but also to each individual’s definition of illness, which in fact differs from the one assumed by their physician.

The identification of cultural issues involved in the suffering of children with juvenile-onset SpA and their relatives should enhance the information obtained by the medical team. Hopefully, the analysis and interpretation of such information should improve our understanding of juvenile-onset SpA not only as a disease affecting the entheses and joints, but as an ‘illness’ that needs a wider therapeutic scope.

Receiving the best available treatment

The treatment of juvenile-onset SpA is therefore complex and is not limited to only pharmacologic and biological therapies. Patients and their relatives should receive information on the efficacy and safety of the therapeutic options available for treating their disease and participate in the decision-making process. They should know, for example, that the efficacy, safety and cost of analgesics and NSAIDs are highly different from those of TNF blockers and decide what would be appropriate for them. Since the course of juvenile-onset SpA may fluctuate and some symptoms might not improve with treatment, patients often stop taking their medications.

Figure 1. Interplay between the three main performers facing the challenges of a chronic inflammatory disabling disease of the synovium and entheses of both the peripheral and axial joints of children and adolescents. Challenges are defined here in a wide sense and confront three different, but inter-related, targets. We propose three models, each confronting challenges in different ways. The patient-centered model is highly oriented to the cultural effect of the disease. The biomedical model refers to the challenge faced by the physician and his/her team. Besides the relationship between the patient and his/her physician, the latter confronts ‘scientific’ and ‘technical’ challenges. Ultimately, in this interplay we consider the ‘disease’ and ‘illness’ as an entity in need of recognition as an individual being.
Patients on TNF blockers have been found to experience an outstanding improvement in their quality of life [19], despite the fact that for some of them the decision of taking TNF blockers was not easy because they were not convinced about their efficacy and safety, or they could not afford their cost.

Challenges for the treating physician & their team

- **Nomenclature & classification criteria**
To date, there are still no satisfactory names, classification or diagnostic and classification criteria for juvenile SpA. The two names currently in use, juvenile-onset SpA and ERA, present two different concepts. The former corresponds to the concept of SpA first developed in the 1970s [24,25]. At that time, the names seronegative polyarthritis, seronegative spondarthritis or seronegative spondyloarthropathies were used to describe a group of inter-related disorders, specifically AS, PsA, Crohn’s disease, ulcerative colitis and ReA, characterized by familial aggregation, *HLA-B27* association, sacroiliitis, enthesopathy and lower-limb arthritis (originally, the group also included Behcet’s disease, uveitis and juvenile chronic polyarthritis). Since 1991, the classification of SpA has relied upon the proposal made by the European Spondyloarthropathy Study Group (ESSG) [26]. Such criteria have been validated in children [27].

Enthesitis-related arthritis refers to one of the subgroups of the classification of JIA developed by the analysis and consensus of a group of experts in juvenile arthritis and endorsed by the International League for Rheumatology Associations (ILAR), the WHO and the American College of Rheumatology (ACR) [28]. While most ERA and SpA inclusion criteria correspond to each other, the list of ERA exclusions may prevent the inclusion of various SpA in the group (Box 1) [29]. Exclusions for the diagnosis of ERA that are relevant to the concept of SpA are psoriasis, or a history of psoriasis in the patient or first-degree relative. As mentioned later, PsA was fundamental for the grouping of AS, ReA (formerly Reiter’s syndrome) and intestinal bowel disease (IBD) arthropathies under terms that subsequently evolved into SpA [30].

The list of exclusion criteria for the diagnosis of PsA in the JIA classification also disagrees with the concept of SpA. According to Vancouver’s criteria, approximately 25% of patients with juvenile-onset PsA do not fulfil ILAR criteria owing to exclusion criteria (Box 2) [31,32]. This certainly contrasts with clinical information. Two subpopulations of juvenile-onset PsA may be distinguished according to age at onset – one occurring around adolescence and another in the early years – differing in demographic and clinical aspects [16,31–36]. The older-age group is mainly composed of boys with persistent oligoarthritis, enthesitis, and clinical and MRI involvement of the sacroiliac and spinal joints some years after onset of disease or in adult life [31–36]; the younger group often includes girls with small joint involvement and asymmetrical polyarthritis throughout the course of the disease, dactylitis and antinuclear antibodies [39]. It is most likely that the clinical features of juvenile-onset PsA do not differ from juvenile-onset AS, but there are no studies comparing such subgroups of patients. By contrast, peripheral disease may affect the upper limb joints, including the small joints of the hands, in more patients with psoriatic SpA than in juvenile-onset AS.

Ultimately, the Assessment of Spondylo-Arthritis International Society (ASAS) has recently developed new criteria for the classification of axial [37,38] and peripheral SpA (work in progress) in adults that incorporate MRI of the sacroiliac joints and *HLA-B27* in the list of criteria – resembling ESSG inclusion criteria – to increase the diagnostic and classification properties of existing criteria. Similarly to ESSG criteria, the new ASAS criteria consider PsA, ReA and IBD arthropathies as part of the SpA spectrum. It is expected that the ASAS criteria would be applicable to children with SpA. Oligoarthritis in *HLA-B27*-positive children with and without sacroiliac symptoms has already been associated with sacroiliitis by MRI [39,40].

- **Differentiating juvenile-onset SpA from other subgroups of JIA**
This process has diagnostic and therapeutic implications since the role of genetic factors, clinical manifestations and drug efficacy differ between clinical forms. Arthritis is usually the more common manifestation at onset in most clinical forms. The pattern of joint involvement, extrarticular manifestations, laboratory findings and demographies help to differentiate one clinical subgroup from another. Distinctive features of juvenile-onset SpA include *HLA-B27*, familial aggregation, enthesopathy, tarsitis, sacroiliac and spinal involvement, anterior uveitis, intestinal bowel disease, psoriasis and infections as triggers [4–6]. By contrast, the prevalence of the following features is either low or absent in patients with juvenile-onset SpA: hand joint involvement at onset, chronic iridocyclitis, evanescent
rash, fever, lymph node as well as spleen and liver enlargement, antinuclear antibodies and rheumatoid factor.

**Comparing juvenile-onset & adult-onset SpA**

Juvenile- and adult-onset SpA differ in some aspects, but, in general, the evidence does not support that they are different diseases. This is particularly true in relation to AS, in which most differences consist of symptoms at onset [41–48]. In contrast to adults, children and adolescents with AS have peripheral arthritis and enthesitis in the initial years and axial symptoms 5–10 years later. The severity of juvenile-onset SpA/AS, except in the spine, is greater in juveniles than in adults since more juveniles require hip replacements, are in functional classes III and IV, and their mean Bath AS functional index scores are higher. Interestingly, a recent study found milder consequences in juvenile-onset AS compared with adult-onset AS [48]. Norwegian and Mexican children with SpA show stronger associations with HLA-DRB1*08 [49,50], HLA-DPB1*0301 and LMP2 [49] gene polymorphism than in adult-onset patients. Slight differences in the histopathological aspect of the synovial membranes between juvenile- and adult-onset SpA have also been described [51]. Ultimately, we considered that juvenile- and adult-onset SpA, mainly AS, are essentially the same disease and differences correspond only to some phenotypical features.

**Identification of prognostic factors**

The identification of factors determining a bad prognosis in children and adolescents with juvenile-onset SpA is of great importance. Structural and rather irreversible changes, such as radiographic sacroiliitis and spondylitis of the AS type, tarsal ankylosis and poor functioning, are associated with HLA-B27, age at onset, disease duration, hip involvement, polyarthrits, or spinal symptoms at onset in univariate and/or multivariate analyses [5–7,14,52–56]. Although this information should be carefully interpreted and confirmed in larger studies, it certainly resembles some of the adult-onset AS data. The identification of factors of bad prognosis may have direct implications in the decision to start and maintain therapies such as TNF blockers in patients with juvenile-onset SpA.

**Designing outcome measures**

Despite the fact that there are no specific outcome measures designed for patients with juvenile-onset SpA [57], the adaptation of those developed for children with JIA and adults with AS might be valid. Data from a randomized, placebo-controlled trial of infliximab suggest that most of JIA and AS outcome measures are useful in children with juvenile-onset SpA [58,59].

**Providing an effective treatment**

Traditionally, the treatment of juvenile-onset SpA derives from the treatment of either patients with adult-onset SpA or other forms of JIA. Very few papers come from case reports or clinical trials on patients with juvenile-onset SpA, and no specific therapeutic recommendations or guidelines for their treatment have been issued. NSAIDs may reduce pain and swelling and consequently improve functioning. Per oral, intrarticular and systemic glucocorticoids in moderate-to-severe cases may be useful in patients not responding to NSAIDs; however, their administration should be carefully considered owing to adverse events. Although few reports suggest some beneficial outcomes with the use of sulfasalazine [60–62], there is no clear evidence of their efficacy in controlling disease activity or

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**Box 1. The European Spondylarthropathy Study Group and the International Associations for Rheumatology classification criteria for spondyloarthropathies and enthesitis-related arthritis subgroup of juvenile idiopathic arthritis.**

**European Spondylarthropathy Study Group (ESSG) classification criteria** [26]

- Inflammatory spinal pain or synovitis, asymmetric or predominantly lower limbs and one or more of the following criteria:
  - Positive family history
  - Psoriasis
  - Inflammatory bowel disease
  - Urethritis, cervicitis or acute diarrhea within 1 month before arthritis
  - Buttock pain alternating between right and left gluteal areas
  - Enthesopathy
  - Radiographic sacroiliitis

**Exclusions:**

- None

**International Associations for Rheumatology (ILAR) proposed classification criteria** [28]

- Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following:
  - The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
  - The presence of HLA-B27 antigen
  - Onset of arthritis in a male over 6 years of age
  - Acute (symptomatic) anterior uveitis
  - History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome or acute anterior uveitis in a first-degree relative

**Exclusions:**

- Psoriasis or a history of psoriasis in the patient or first-degree relative
- The presence of IgM rheumatoid factor on at least two occasions at least 3 months apart

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Challenges in juvenile-onset spondyloarthritis
Box 2. The Vancouver’s and the International Associations for Rheumatology classification criteria for juvenile psoriatic arthritis subgroup of juvenile idiopathic arthritis.

**Vancouver’s definition of PsA** [32]
- Arthritis and psoriasis
- Arthritis and at least two of the following:
  - Psoriasis
  - Family history of psoriasis
- Probable juvenile PsA
- Arthritis plus two of the minor criteria
- Exclusions:
  - None

**International Associations for Rheumatology (ILAR) definition of PsA** [28]
- Arthritis and psoriasis
- Arthritis and at least two of the following:
  - Dactylitis
  - Nail pitting
  - Psoriasis
  - Probable juvenile PsA
- Arthritis plus at least three of four minor criteria:
  - Dactylitis
  - Nail pitting
  - Psoriasis
  - Family history of psoriasis
- Definite juvenile PsA

JIA: Juvenile idiopathic arthritis; PsA: Psoriatic arthritis.

Inducing sustained remission for such a drug or methotrexate, which is also frequently used in juvenile-onset SpA.

Although specific recommendations to start TNF blockers in patients with juvenile-onset SpA are lacking, both severe and persistent disease activity and failure to respond to NSAIDs and perhaps sulfasalazine would be appropriate indications for TNF therapy. Indeed, we need to define each of those items according to an expert’s opinion and literature review. The efficacy and safety of etanercept and infliximab have been shown in small open series of patients [63–65] and in an infliximab/placebo-controlled trial of 3 months followed by a 54-week open extension [58,59]. The effect of TNF blockers is rapid and sustained while patients continue treatment; their interruption might follow one of two possibilities: sustained remission off TNF blockers or flare-up of the disease within 6 months. Work in progress suggests that the duration of the disease at the start of TNF blockers determines the course post-treatment; patients with short duration of the disease have longer remission off TNF blockers. This is a relevant issue because patients like to know how long they should be on TNF therapy for after reaching remission so they can avoid adverse events from its long-term use.

Unfortunately, at present there is no information to support the abrogation of structural damage – namely joint or enthesis erosions or bone proliferation – induced by TNF blockers. Data from adult-patient cohorts suggest slow but continuous progression of structural changes of the spine on radiographs up to 5 years after initiation of continuous treatment [66–68]. Studies in animal models support the concept that TNF blockers do not inhibit new bone formation [69–71]. By contrast, TNF stimulates osteoclast and bone resorption. TNF blockade, however, does not prevent ankylosis, but is likely to inhibit erosive joint and bone damage. The two outcomes are important for the patients. TNF induces Dickkopf-1 (DKK1), which then inhibits Wnt/β-catenin and new bone formation. The mechanisms involved in such effects are DKK1 osteoclast stimulation and new bone formation through osteoprotegerin [72]. TNF blockade results in inhibition of DKK1, but not of Wnt/β-catenin, and, consequently, bone formation occurs. These effects change the phenotype of mouse arthritis from destructive to remodeling. However, there is currently no experimental or clinical evidence that inhibition of TNF would lead to accelerated or expanded ankylosis. The remarkable improvement of TNF-α-mediated inflammatory signs and symptoms in children and adolescents with SpA treated with TNF blockers may not be sufficient to halt disease progression. Thus, the idea of developing an additional therapy to prevent bone proliferation should be considered.

Adverse events are usually mild and transitory and consist of an increased prevalence of upper tract infections and of local or systemic reactions to administration of TNF blockers. Despite the fact that there are only a few reports of severe adverse events associated with TNF blockers, the US FDA has recently issued a black box warning on the possibility of lymph node malignancies in children being treated with this therapy [73]. Since the US FDA warning lacks significant details, the interpretation of such a warning should be very careful.

**Juvenile-onset SpA challenges**

- Recognition of juvenile-onset SpA as a clinical entity

According to Bywaters [74,75] the first clinical description of AS corresponded to that of Benjamin Travers of Saint Thomas’ Hospital.
UK, who reported on a ‘curious case of ankylosis, of a great part of the vertebral column, probably produced by an ossification of the intervertebral substance’ in The Lancet [76]. In that particular patient, stiffness started at the age of 16 years and by the age of 19 years she had ankylosis from the neck down to ossification of the ‘intervertebral substance’. There were no further references to AS starting in childhood or adolescence and no mention of such a clinical picture in the historic descriptions of juvenile arthritis or AS made at the end of the 1800s [74,75,77]. Interestingly, Scott – a radiologist with an interest in AS – in 1942 published the book A Monograph on Adolescent Spondylitis or Ankylosing Spondylitis, the Early Diagnosis and its Treatment by Wide-Field X-ray Irradiation, in which he described several cases of AS starting in adolescence and considered AS a disease of very young people [78]. Scott’s remarks included the need for early diagnosis to halt disease progression by using wide-field x-ray radiation. However, it was not until 1959, when Ansell and Bywaters considered AS as one of various outcomes of Still’s disease [79], that case reports involving a small series of patients with juvenile AS were published.

In 1973, Brewerton et al. [80] and Scholstein et al. [81] described the association between HLA-B27 (formerly HL-A27 and HL-AW27) and AS. Approximately 1 year later, Edmonds et al. reported the positive association of HLA-B27 with juvenile AS and juvenile chronic polyarthritis (JCP) linked to sacroiliitis as well as the negative association of such antigen with rheumatoid factor negative and positive JCP subgroups [52]. The association between HLA-B27 and JRA, particularly in older children with oligoarthritis, was later confirmed [82,83]. Thus, it was not only juvenile AS, but also an entity characterized by oligoarthritis, sacroilitis of the AS type and HLA-B27 in children – mostly boys around the age of 10 years – that was soon recognized.

In Ansell and Wood’s classification of JCP, ‘polyarthritis with AS type sacroilitis’ was second on the list of JCP clinical subgroups [84]. Still’s disease, with the systemic, polyarticular and pauciarticular – with or without chronic iridocyclitis – variants was the most important clinical subgroup in that classification. Interestingly, PsA and IBD arthritis were also separated from the three subtypes of Still’s disease. JRA classification [85], which was certainly equivalent to Still’s disease, considered AS in the list of diagnostic exclusions.

By the end of the 1970s, when the concept of seronegative spondarthritis in the adult patient population was well established [86], AS and in particular AS-like JCP (JCP with sacroilitis of the AS type) and JRA (oligo JRA II) were in the process of recognition.

Since clinicians found difficulties in interpreting the radiographic films of the sacroiliac joints of children – attributed to bone development – attempts to develop diagnostic criteria for AS in children were developed [87,88]. Such criteria essentially referred to nonaxial, nonradiographic elements to make the diagnosis of AS, but none were used in clinical practice.

In 1982, Jacobs et al. [89] and Rosenberg and Petty [6] incorporated the clinical hallmark of SpA, enthesopathy, as the key element in the clinical description of the ‘HLA-B27 associated spondyloarthritis and enthesopathy in childhood’ and the ‘seronegative enthesopathy and arthropathy syndrome’. The description of these two forms of disease ultimately expanded the spectrum of SpA and increased their recognition in specialized clinics. During the following years, a number of publications described short- and long-term follow-ups of children with undifferentiated SpA, disease activity, physical functioning, HRQoL as well as some aspects in their pathogenesis and treatment.

In resemblance to adult-onset SpA classification, PsA, IBD and ReA (which in most descriptions was named Reiter’s syndrome) were grouped with seronegative enthesopathy and arthropathy syndrome and AS in children under the term juvenile SpA [90]. In parallel with these advances, attempts to better define AS were made by several authors by determining whether or not juvenile and adult forms corresponded to the same disease [41–44].

At the end of the 1990s, a new classification of juvenile arthritis endorsed by ILAR, the WHO and ACR, and last reviewed in 2004, proposed seven clinical subgroups of JIA, including one resembling juvenile-onset SpA, ERA, and another for PsA [28]. JIA classification did not consider the ERA and PsA relationship and, in fact, the diagnosis of one category excluded the other.

Nevertheless, there is no doubt at the end of the first decade of 2000 that juvenile-onset SpA has surpassed the challenge of ‘being’ and is now recognized either as SpA or ERA, as the juvenile or childhood equivalent of adult SpA or a different subgroup of chronic arthritis.

Conclusion & future perspective
The purpose of this article was to identify challenges in juvenile-onset SpA and, when possible, propose solutions to them. We took advantage of the broad definition of the word ‘challenge’ and approached the topic from our own perspective.
According to that, we recognized three main elements: the patient, the physician and the disease. Each of these elements faces specific and general challenges. Likewise, the strategies to overcome each of these challenges may be specific for each of the three elements or those shared by them. Ultimately, we recognized three models of challenge interplaying in juvenile-onset SpA: the patient-centered model, which is highly oriented to the cultural effect of the disease; the biomedic model, which refers to the challenge faced by the physician and their team; and the ‘disease’ and ‘illness’ as entities in need of recognition.

To confront the challenges faced by the patient, the physician and the disease, and outline the strategies to solve such challenges, we should recognize the existence of such three models of challenge and understand that they should be seen from a different perspective. Our future approach would then be best directed to solve both specific and general challenges.

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No writing assistance was utilized in the production of this manuscript.

### Executive summary

**Juvenile-onset spondyloarthropathies**
- A group of diseases characterized by familial aggregation, HLA-B27 association, peripheral arthritis and enthesitis, as well sacroiliitis and spondylitis in some cases.

**Challenges in juvenile spondyloarthropathies**
- From our own perspective, we have identified three elements presenting challenges: patients and relatives, the treating physician and their medical team, and the disease itself.

**Patients’ & relatives’ challenges**
- Benefit from an early diagnosis and best available treatment.
- Prevent and overcome the physical consequences of the disease.
- Identify and intervene to lessen the role of cultural factors.

**Physician challenges**
- Set working groups to produce better concepts, definitions and classification of this group of disorders.
- Design cohort studies to better understand the natural history of juvenile-onset spondyloarthritis, identify prognostic factors and design outcome measures.
- Develop clinical trials to determine drug efficacy and safety.
- Produce therapeutic recommendations.

**Disease challenges**
- Recognition as an important groups of rheumatic diseases in children.

### Bibliography

Papers of special note have been highlighted as:
- of interest
- of considerable interest


**Excellent paper on the role of certain factors in determining the prognosis of enthesitis-related arthritis (ERA).**


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**Refers to the development of the European Spondyloarthropathy Study Group (ESSG) classification criteria for spondyloarthropathy.**


**Refers to the development of the juvenile idiopathic arthritis classification criteria, including enthesitis-related arthritis (ERA) and psoriatic arthritis (PsA).**


**Refers to the development of the Vancouver’s diagnostic criteria of PsA in children.**


* Describes two subtypes of juvenile PsA.


Burgos-Vargas, Peláez-Ballestas & Gutiérrez-Suárez

**Challenges in juvenile-onset spondyloarthritis**

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