The objective of this guide is to provide a summary of the ACR 2011 Recommendations for the Treatment of juvenile idiopathic arthritis, which have been reviewed and endorsed by the Arthritis Foundation. This guide is not intended to be used as a stand-alone document and should be used in conjunction with the full manuscript published in the April 2011 issue of Arthritis Care and Research.

Purpose and methodology

The treatment of juvenile idiopathic arthritis has benefitted from several recent major advances; however, to date, no validated guidelines offer recommendations for the treatment of JIA. To develop recommendations for the safest and most effective treatment of JIA, the established RAND/UCLA Appropriateness Method was applied to derive recommendations that are as evidenced-based as possible with the understanding that the published literature often does not provide evidence at the level of detail required to guide decisions in everyday clinical practice. The RAND/UCLA process aims to determine which medical interventions are “appropriate,” which is defined as when the health benefits exceed the health risks by a sufficiently wide margin that the intervention is worthwhile. Details of the development of the recommendations can be found in the full manuscript.

Scope

These recommendations cover the initiation and safety monitoring of therapeutic agents in the treatment of JIA, including non-steroidal anti-inflammatory drugs, intra-articular glucocorticoid injections, non-biologic disease modifying anti-rheumatic drugs, biologic DMARDs, and systemic glucocorticoids for the treatment of the systemic features of systemic arthritis. Of note, these recommendations divide JIA into ‘treatment groups’ instead of the JIA categories set forth by International League of Associations for Rheumatology.

These recommendations were developed with international input and are intended to inform and benefit health care providers caring for children with JIA throughout the world. Many recommendations fall outside the present bounds of regulatory agency approved labeling, but reflect common and widely accepted practices in the field.

Therapies that were approved after the original literature review are not included in these recommendations.

Rating the strength of evidence

The levels of evidence associated with the recommendations, as determined using the University of Oxford Centre for Evidence Based Medicine method, are provided in the full manuscript. The levels include:

- **Level A** = randomized clinical trials
- **Level B** = non-randomized controlled studies (e.g., cohort and case-control studies) or extrapolations from randomized clinical trials
- **Level C** = uncontrolled studies (case series), extrapolations from non-randomized controlled studies, or marked extrapolations from randomized clinical trials
- **Level D** = expert opinion without supporting published evidence
Initiation of specific therapeutic agents

Four key clinical parameters are defined for each recommendation: JIA treatment group, current treatment, disease activity, and features of poor prognosis. The five JIA treatment groups include:

- **History of arthritis of four or fewer joints.** This group includes patients with the ILAR categories of persistent oligoarthritis, as well as patients with psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis who have developed active arthritis in only four or fewer joints total throughout the history of their disease course.

- **History of arthritis of five or more joints.** This group includes patients with the ILAR categories of extended oligoarthritis, RF negative polyarthritis, RF positive polyarthritis, as well as patients with psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis who have developed active arthritis in five or more joints total throughout the history of their disease. Patients in this group need not currently have five or more active joints.

- **Active sacroiliac arthritis.** This group includes all patients with clinical AND imaging evidence of active sacroiliac arthritis. May include patients from any of the ILAR JIA categories.

- **Systemic arthritis with active systemic features (and without active arthritis).** This group includes all patients who fulfill the ILAR criteria for systemic arthritis AND who have active fever of systemic JIA with or without other systemic features, but without active arthritis.

- **Systemic arthritis with active arthritis (and without active systemic features).** This category includes all patients who fulfill the ILAR criteria for systemic arthritis AND who have active arthritis, but without active systemic features.

Disease activity levels and features of poor prognosis are specific to each JIA treatment group and are listed in Tables 1 through 5.

### Table 1. Features of poor prognosis and disease activity for a history of arthritis of 4 or fewer joints

<table>
<thead>
<tr>
<th>Features of Poor Prognosis (must satisfy 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis of the hip or cervical spine</td>
</tr>
<tr>
<td>Arthritis of the ankle or wrist AND marked or prolonged inflammatory marker elevation</td>
</tr>
<tr>
<td>Radiographic damage (erosions or joint space narrowing by radiograph)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Activity Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Disease Activity</strong></td>
</tr>
<tr>
<td><strong>Moderate Disease Activity</strong></td>
</tr>
<tr>
<td><strong>High Disease Activity</strong></td>
</tr>
</tbody>
</table>

- **Low Disease Activity (must satisfy all)**
  - 1 or fewer active joints
  - Erythrocyte sedimentation rate or C-reactive protein level normal
  - Physician global assessment of overall disease activity < 3 of 10
  - Patient/parent global assessment of overall well-being < 2 of 10

- **Moderate Disease Activity (does not satisfy criteria for low or high activity)**
  - 1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity

- **High Disease Activity (must satisfy at least 3)**
  - 2 or more active joints
  - Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
  - Physician global assessment of overall disease activity ≥ 7 of 10
  - Patient/parent global assessment of overall well-being ≥ 4 of 10
### Table 2. Features of poor prognosis and disease activity for a history of arthritis of 5 or more joints

<table>
<thead>
<tr>
<th>Features of Poor Prognosis (must satisfy 1)</th>
<th>Moderate Disease Activity (does not satisfy criteria for low or high activity)</th>
<th>High Disease Activity (must satisfy at least 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis of the hip or cervical spine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive rheumatoid factor OR anti-cyclic citrullinated peptide antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic damage (erosions or joint space narrowing by radiograph)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Disease Activity Levels**

<table>
<thead>
<tr>
<th>Low Disease Activity (must satisfy all)</th>
<th>Moderate Disease Activity (does not satisfy criteria for low or high activity)</th>
<th>High Disease Activity (must satisfy at least 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 or fewer active joints</td>
<td>1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity</td>
<td>8 or more active joints</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate or C-reactive protein level normal</td>
<td></td>
<td>Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal</td>
</tr>
<tr>
<td>Physician global assessment of overall disease activity &lt; 4 of 10</td>
<td></td>
<td>Physician global assessment of overall disease activity ≥ 7 of 10</td>
</tr>
<tr>
<td>Patient/parent global assessment of overall well-being &lt; 2 of 10</td>
<td></td>
<td>Patient/parent global assessment of overall well-being ≥ 5 of 10</td>
</tr>
</tbody>
</table>

### Table 3. Feature of poor prognosis and disease activity for active sacroiliac arthritis

<table>
<thead>
<tr>
<th>Feature of Poor Prognosis</th>
<th>Moderate Disease Activity (does not satisfy criteria for low or high activity)</th>
<th>High Disease Activity (must satisfy at least 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic damage of any joint (erosions or joint space narrowing by radiograph)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Disease Activity Levels**

<table>
<thead>
<tr>
<th>Low Disease Activity (must satisfy all)</th>
<th>Moderate Disease Activity (does not satisfy criteria for low or high activity)</th>
<th>High Disease Activity (must satisfy at least 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal back flexion</td>
<td>1 or more features greater than low disease activity level AND fewer than 2 features of high disease activity</td>
<td>Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate or C-reactive protein level normal</td>
<td></td>
<td>Physician global assessment of overall disease activity ≥ 7 of 10</td>
</tr>
<tr>
<td>Physician global assessment of overall disease activity &lt; 4 of 10</td>
<td></td>
<td>Patient/parent global assessment of overall well-being ≥ 4 of 10</td>
</tr>
<tr>
<td>Patient/parent global assessment of overall well-being &lt; 2 of 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Feature of poor prognosis and disease activity for systemic arthritis with active systemic features (and without active arthritis)

<table>
<thead>
<tr>
<th>Features of Poor Prognosis</th>
<th>Disease Activity Levels (2 levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids</td>
<td>Active fever AND physician global assessment of overall disease activity &lt; 7 of 10</td>
</tr>
<tr>
<td>Active fever AND systemic features of high disease activity (e.g., significant serositis) that result in physician global assessment of overall disease activity ≥7 of 10</td>
<td>Active fever AND systemic features of high disease activity (e.g., significant serositis) that result in physician global assessment of overall disease activity ≥7 of 10</td>
</tr>
</tbody>
</table>
Current treatment is depicted directly in the recommendation figures. For all recommendations, it is assumed that patients have received the maximum tolerated typical dose of prior medications, as listed in Supplementary Appendix B. Of note, the dose of methotrexate is assumed to be 15 mg/m² (0.6 mg/kg) and administered via the parenteral route. For recommendations in which duration of therapy is not defined, it is assumed that the duration of therapy is sufficiently long to assess the response to therapy.

Figures 1 through 4 depict the recommendations for initiation of therapeutic agents for the treatment of JIA. Therapy is escalated as one moves downward in each figure. If the key clinical parameter criteria listed for escalation of therapy are not met, then the recommendation is to continue current therapy along with adjunct NSAID or glucocorticoid joint injections as needed. Recommendations for reduction of therapy are not addressed.

**Table 5.** Features of poor prognosis and disease activity for systemic arthritis with active arthritis (and without active systemic features)

<table>
<thead>
<tr>
<th>Features of Poor Prognosis (must satisfy 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis of the hip</td>
</tr>
<tr>
<td>Radiographic damage (erosions or joint space narrowing by radiograph)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Activity Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Disease Activity (must satisfy all)</strong></td>
</tr>
<tr>
<td>4 or fewer active joints</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate or C-reactive protein level normal</td>
</tr>
<tr>
<td>Physician global assessment of overall disease activity &lt; 4 of 10</td>
</tr>
<tr>
<td>Patient/parent global assessment of overall well-being &lt; 2 of 10</td>
</tr>
<tr>
<td><strong>Moderate Disease Activity (does not satisfy criteria for low or high activity)</strong></td>
</tr>
<tr>
<td>1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity</td>
</tr>
<tr>
<td><strong>High Disease Activity (must satisfy at least 3)</strong></td>
</tr>
<tr>
<td>8 or more active joints</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal</td>
</tr>
<tr>
<td>Physician global assessment of overall disease activity ≥ 7 of 10</td>
</tr>
<tr>
<td>Patient/parent global assessment of overall well-being ≥ 5 of 10</td>
</tr>
</tbody>
</table>

**History of Arthritis of 4 or Fewer Joints**

- **Following 2 months NSAID:**
  - Disease Activity: Low
  - Poor Prognostic Features: Irrespective

- **Following Initial Joint Injection(s):**
  - Disease Activity: Moderate
  - Poor Prognostic Features: Present
  - OR: Disease Activity: High
  - Poor Prognostic Features: Irrespective

- **Following Repeat Joint Injection(s):**
  - Disease Activity: Low
  - Poor Prognostic Features: Present
  - OR: Disease Activity: Moderate
  - Poor Prognostic Features: Irrespective

- **Following 3 months MTX:**
  - Disease Activity: Moderate or High
  - Poor Prognostic Features: Present

- **Following 6 months MTX:**
  - Disease Activity: High
  - Poor Prognostic Features: Irrespective

- **TNFα inhibitor**
  - Adjunct NSAID or Joint Injection as needed

- **Methotrexate**
  - Adjunct NSAID or Joint Injection as needed

- **Glucocorticoid Joint Injection(s)**
  - Adjunct NSAID as needed

- **NSAID monotherapy**
  - Following 2 months NSAID:
    - Disease Activity: Low
    - Poor Prognostic Features: Irrespective
Figure 2. Treatment recommendations for patients with a history of arthritis of 5 or more joints. These recommendations are intended for patients with juvenile idiopathic arthritis who have developed active arthritis in 5 or more joints in total throughout the history of their disease and are based upon duration of current therapy, disease activity, and features of poor prognosis. If criteria for escalation of therapy are not met, then continue current therapy along with adjunct nonsteroidal antiinflammatory drugs (NSAIDs) or glucocorticoid joint injections, as needed. Recommendations for reduction of therapy are not addressed. See Table 2 for definitions of disease activity and features of poor prognosis. *=leflunomide may be an appropriate treatment alternative (see text in full paper for details); MTX=methotrexate; TNF= tumor necrosis factor α.

Figure 3. Treatment recommendations for patients with systemic arthritis and active systemic features (and without active arthritis). These recommendations are intended for patients with juvenile idiopathic arthritis who have systemic arthritis with active systemic features and without active arthritis. Recommendations are based upon duration of current therapy, disease activity, and features of poor prognosis. If criteria for escalation of therapy are not met, then continue current therapy along with adjunct nonsteroidal antiinflammatory drugs (NSAIDs), as needed. Recommendations for reduction of therapy are not addressed. See Table 4 for definitions of disease activity and features of poor prognosis. MD Global=physician global assessment of overall disease activity (range 0–10).
The recommendations for active sacroiliac arthritis are summarized below.

**Recommendations for patients with active sacroiliac arthritis**

Initiation of TNFα inhibitor is recommended for patients who satisfy the following key clinical parameter criteria:

<table>
<thead>
<tr>
<th>Prior Treatment</th>
<th>Disease Activity</th>
<th>Features of Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate trial of NSAIDs</td>
<td>High</td>
<td>Present</td>
</tr>
<tr>
<td>Methotrexate for 3 months</td>
<td>High</td>
<td>Irrespective</td>
</tr>
<tr>
<td>Methotrexate for 3 months</td>
<td>Moderate</td>
<td>Present</td>
</tr>
<tr>
<td>Methotrexate for 6 months</td>
<td>Moderate</td>
<td>Absent</td>
</tr>
<tr>
<td>Sulfasalazine for 3 months</td>
<td>Moderate or high</td>
<td>Irrespective</td>
</tr>
<tr>
<td>Sulfasalazine for 6 months</td>
<td>Low</td>
<td>Present</td>
</tr>
</tbody>
</table>
Safety monitoring

The recommendations for medication safety monitoring are summarized in Table 6.

Table 6. Summary of recommendations for medication safety monitoring

<table>
<thead>
<tr>
<th>Safety monitoring</th>
<th>Non-steroidal anti-inflammatory drugs (NSAIDs)</th>
<th>Methotrexate</th>
<th>Tumor Necrosis Factor α Inhibitors</th>
<th>Tuberculosis screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete blood cell count, liver enzymes, serum creatinine</td>
<td>Complete blood cell count, liver enzymes, serum creatinine</td>
<td>Complete blood cell count, liver enzymes, serum creatinine</td>
<td>Complete blood cell count, liver enzymes, serum creatinine</td>
</tr>
<tr>
<td></td>
<td>• Prior to or soon after initiation of routine use</td>
<td>• Prior to initiation</td>
<td>• Prior to initiation</td>
<td>• Prior to initiation</td>
</tr>
<tr>
<td></td>
<td>• Repeat approximately twice yearly for chronic daily use</td>
<td>• Approximately 1 month after initiation</td>
<td>• Approximately 1–2 months after increase in dose</td>
<td>• Repeat approximately once yearly</td>
</tr>
<tr>
<td></td>
<td>• Repeat approximately once yearly for routine use (3-4 days per week)</td>
<td>• Repeat approximately every 3-4 months if prior results normal and dose stable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notable Recommendations for Initiation of Biologic Agents

<table>
<thead>
<tr>
<th>JIA Treatment Group</th>
<th>Initiate TNF-α inhibitor if significant arthritis proves refractory to methotrexate</th>
<th>Initiate TNF-α inhibitor if low disease activity remains following 6 months of optimal methotrexate</th>
<th>Initiate abatacept if inadequate response to TNF-α inhibitor</th>
<th>Lower threshold for initiation of TNF-α inhibitor compared to patients without active sacroiliac arthritis</th>
<th>Initiate anakinra as the first steroid-sparing agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of 4 or fewer active joints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of 5 or more active joints</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Active sacroiliac arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active systemic features (fever)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

For more information

For electronic copies of the Clinician’s Guide, the full guideline, or details about the evidence review and guideline development process, click here or reference the April 2011 issue of Arthritis Care and Research.

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