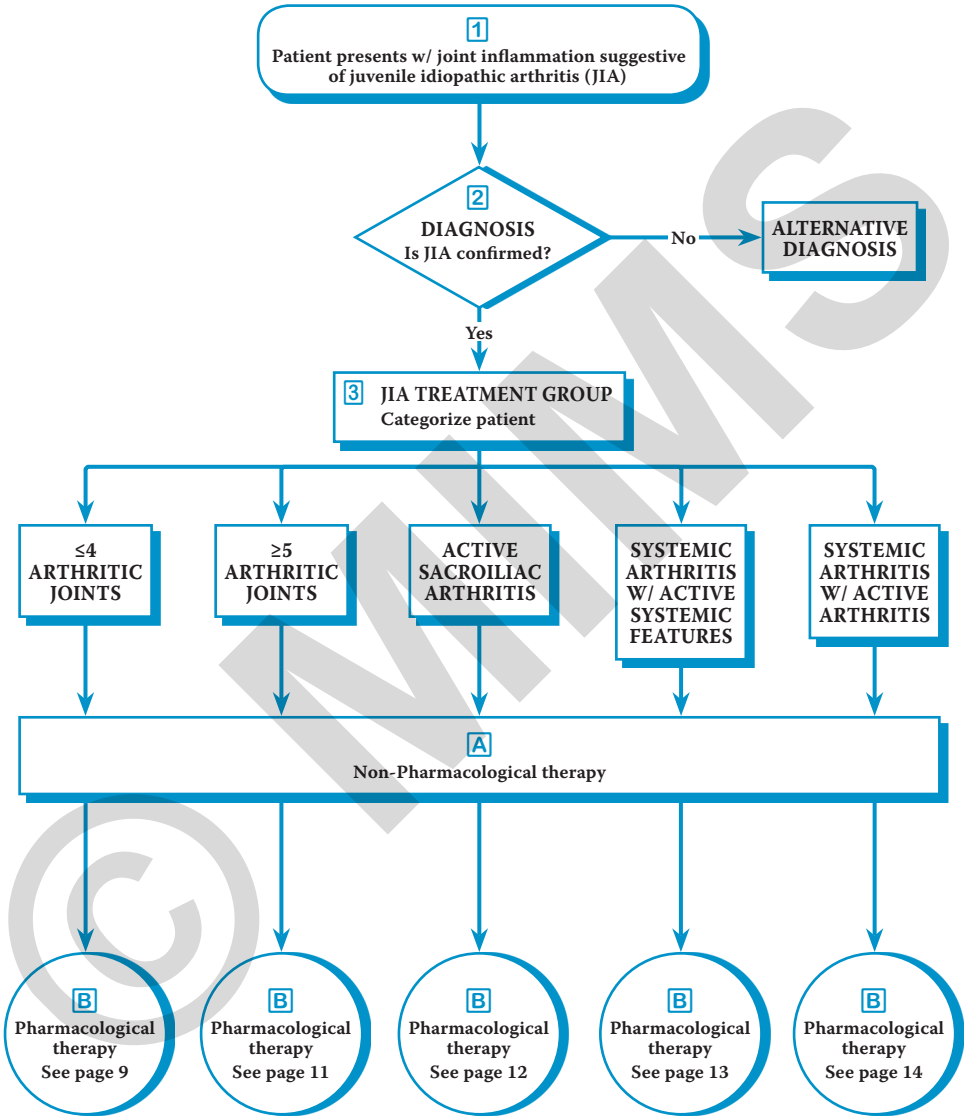
Juvenile Idiopathic Arthritis (1 of 23)



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1 JUVENILE IDIOPATHIC ARTHRITIS (JIA)

- Formerly known as juvenile rheumatoid arthritis or juvenile chronic arthritis
- Presents w/ arthritis of unknown cause that starts before age of 16 years & persists for at least 6 weeks after ruling out other diseases
  - Arthritis is a condition where there is joint effusion & has decreased range of motion, pain on movement &/or warmth on the joint
- Most common autoimmune-autoinflammatory disease in children
- Differs from rheumatoid arthritis of the adults in terms of age at presentation, propensity to cause joint contractures & muscle wasting, & association w/ extraarticular manifestation
- Around 50% of children w/ JIA may have active disease until adulthood

2 DIAGNOSIS

- An early & accurate diagnosis is important to start the correct management to promote normal growth & development, & to lessen disability & deformity
  - Excessive delay in diagnosis causes late treatment that leads to severe damage of joints & other organs, & impairs skeletal maturation

History & Physical Exam

- Mainly the basis of JIA diagnosis
- JIA is highly considered in patients w/:
  - Pain & swelling of ≥1 joints; some children may not complain of pain but is usually elicited by active or passive motion
    - Constant or progressive loss of function
    - At least 10 days duration of fever that has no known cause & is often associated w/ transient erythematous rash
    - High spiking fever (≥39°C) w/ a quotidian pattern is the most recognized feature of systemic involvement
    - Lesions are most commonly seen in the trunk & proximal extremities & usually consists of discrete, circumscribed, salmon-pink 2-10 mm sized macules that may be surrounded by a ring of pallor or may develop central clearing & is usually evanescent w/ fever spikes; may be elicited by rubbing &/or scratching the skin (Koebner response), by hot bath, or by psychological stress
    - Reduced range of motion
    - Warm joints
    - Effusion
  - Patient may have complaints of morning stiffness & gelling after inactivity or swelling of affected joint after trauma
  - Any joint may be involved but large joints are more commonly affected than the smaller joints
    - Arthritis in large joints causes initial linear growth acceleration that leads to longer affected limb; constant inflammation stimulates rapid & premature closure of the growth plate that results in shortened bones
    - Cricoarytenoid arthritis is uncommon but may cause acute airway obstruction
    - Anterior atlantoaxial subluxation & impaction in the upper cervical spine is often observed rendering the affected child at risk of injury due to accident or intubation
  - Patients may also present w/ scoliosis, small outpouchings of synovium at the extensor hood of the proximal interphalangeal joint around the wrist or ankle, or synovial cyst in the antecubital fossa or anterior to the shoulder
- Extra-articular manifestations include ocular, cardiac, pulmonary & hematopoietic involvement
  - Uveitis is the most common JIA extra-articular manifestation which involves the anterior chamber, affecting 9% of all JIA patients (ie 15-20% of patients w/ oligoarthritis, 5-10% of those w/ polyarthritis, & rarely in patients w/ systemic-onset JIA)
  - 90% occur within 4 years of JIA diagnosis & is usually asymptomatic at onset but may eventually cause posterior synechiae, cataract, band keratopathy, glaucoma, or macular edema
  - Growth failure is more commonly seen in patients w/ systemic arthritis due to its high inflammatory nature & repeated use of long-term oral glucocorticoid agents

2 DIAGNOSIS (CONT'D)

Diagnostic Procedures

- Helpful in increasing accuracy of the diagnosis, classifying the disease, ruling out other types of arthritis, predicting the progression of patient's condition to an erosive type, & monitoring progression of the disease
  - Only supportive in diagnosing JIA since results may be normal
- Advised in patients who present w/ symptoms of >4 weeks duration

Lab Exam

- Erythrocyte sedimentation rate (ESR) & C-reactive protein (CRP)
  - Inflammatory markers but have low specificity for JIA
    - ESR may be helpful in measuring active disease at onset & during follow up visits, especially in patients w/ polyarticular or systemic-onset JIA
    - May be used to monitor disease activity & treatment response
- Rheumatoid factor (RF)
  - Inconclusive test since present in only small percentage of patients w/ JIA
  - Recommended in patients w/ polyarthritis
  - Positive result may indicate possibility of an aggressive disease & poorer prognosis
- Complete blood count (CBC)
  - May help identify presence of inflammation or anemia
    - Microcytic anemia may be present & attributable to chronic disease
    - Leukocytosis may be seen in children w/ active disease & platelet count elevated in severe systemic or polyarticular involvement
- Antinuclear antigen (ANA)
  - Should be assessed in all JIA patients
    - Identifies the risk for the development of asymptomatic uveitis, especially in patients w/ oligoarticular-onset disease
    - Present in 40-50% of patients w/ polyarthritis, 70-85% of patients w/ oligoarthritis, 10% of patients w/ systemic JIA & negative in patients w/ enthesitis-related JIA
    - Risk for chronic uveitis is increased w/ ANA seropositivity
- Human leukocyte antigen (HLA)-B27
  - May be used in diagnosing patients w/ enthesitis-related arthritis
  - May indicate risk for the development of axial arthritis
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies
  - May indicate severe disease but may not be advised in all patients
- Others: double-stranded DNA (dsDNA), extractable nuclear antigens (ENA), C3, C4 & immunoglobulin (Ig)
  - May be helpful if the arthritis is part of an underlying connective tissue disease or vasculitis
  - Studies have showed that serum levels Ig correlate w/ disease activity & acute phase response

Diagnostic Imaging

- Plain radiographs
  - Less costly, easily available & faster way to evaluate joints but limited & nonspecific for early JIA changes
  - Helps identify erosions which is apparent in a disease of >3 months duration
  - May be used to rule out other diagnosis & to confirm clinical findings
  - Soft tissue swelling, periarticular osteoporosis & periosteal new-bone apposition around affected joints are the early radiographic changes of arthritis
  - Subchondral erosions, loss of cartilage, different degrees of bone destruction & bone fusion may be seen in x-rays of patients w/ continued active JIA
  - Serial x-rays may show disease progression & may indicate the need for change in patient's management
- Ultrasound
  - May be used to confirm joint effusions, specifically in the hip & shoulder joints where fluid is often difficult to see clinically
- Magnetic resonance imaging (MRI)
  - More sensitive to early changes than x-rays
  - Identifies inflammatory changes in the joint & damages in the cartilage, & assesses early changes in the soft-tissue
  - Also accurate in evaluating late manifestations of JIA (ie erosions, loss of joint space, damage in the cartilage & involvement of ligaments)
- Technetium-99 bone scan
  - May also help in detecting early stage of inflammatory arthritis

2 DIAGNOSIS (CONT'D)

Classification of JIA

- Developed by the International League of Associations for Rheumatology (ILAR) which includes all subtypes of chronic juvenile arthritis
  - Different to the classification criteria of the American College of Rheumatology (ACR) where the disease was divided according to treatment groups
- Provides important outline for research, helps identify proper management for patients, & predicts the natural history of the disease

SUBTYPE	PEAK AGE OF ONSET	DIAGNOSTIC FEATURES	OTHER FEATURES
Oligoarthritis - Persistent	2-4 years	• Affects ≤4 joints throughout course of disease	• 30% presents w/ uveitis • Lab test: 60% w/ positive ANA; some w/ mild elevation in ESR/CRP; other test may be normal
Oligoarthritis - Extended		• Affects >4 joints after the 1st 6 months of disease	
Polyarthritis - RF-negative	2-4 years & 10-14 years	• Affects ≥5 joints in the 1st 6 months of disease w/ negative RF	• 10% RF-negative patients present w/ uveitis; 10% RF-positive patients have rheumatoid nodules • Lab test: mild-moderate elevation in ESR; normal-mild increase in CRP; mild anemia; 40% RF-negative patients w/ positive ANA
Polyarthritis - RF-positive	9-12 years	• Affects ≥5 joints in the 1st 6 months of disease w/ ≥2 positive RF tested at least 3 months apart	
Systemic-onset	1-5 years	• Affects ≥1 joints w/ or preceded by fever of at least 2 weeks duration w/ quotidian pattern for at least 3 days, *plus* ≥1 of the following: - Transient erythematous rash - Generalized enlargement of lymph nodes - Hepatomegaly - Splenomegaly - Pericarditis ± pleuritis ± peritonitis	• Lab test: anemia; increase in WBC, platelets, ESR, CRP, ferritin
Enthesitis-related arthritis	9-12 years	• Arthritis ± enthesitis *plus* ≥2 of the following: - Presence or history of sacroiliac joint tenderness &/or inflammatory lumbosacral pain - Positive HLA-B27 antigen - Onset of arthritis in male >6 years old - Acute anterior uveitis - History of ankylosing spondylitis, enthesitis-related arthritis, sacroilitis w/ inflammatory bowel disease, Reiter syndrome, or family history of acute anterior uveitis in a 1st-degree relative	• May have acute anterior uveitis, some w/ associated reactive arthritis or inflammatory bowel disease • Lab test: 80% w/ positive HLA-B27
Psoriatic arthritis	2-4 years & 9-11 years	• Arthritis ± psoriasis *plus* ≥2 of the following: - Dactylitis - Nail pitting & onycholysis - 1st-degree relative w/ psoriasis	• 10% presents w/ uveitis; 50% w/ psoriasis • Lab test: 50% w/ positive ANA; mild elevation in ESR/CRP; mild anemia
Undifferentiated arthritis		• Arthritis that does not fit into any or in ≥2 of the above categories	

Modified from: Wu EY, Rabinovich CE. Juvenile idiopathic arthritis. In: Kliegman RM, St. Geme JW, Blum NJ, et al. Nelson Textbook of Pediatrics. 21st ed. Philadelphia, PA, USA: Elsevier; 2019.

3 JIA TREATMENT GROUP

- Management of JIA patients were based on their treatment groups since there are few evidence to support the differential treatment of children w/ JIA for different category distinctions
  - Based on patient's disease activity level & presence or absence of poor prognostic features

JIA TREATMENT GROUP	JIA SUBTYPE	FEATURES OF POOR PROGNOSIS (must satisfy at least 1)	DISEASE ACTIVITY LEVELS		
			LOW (must satisfy all)	MODERATE (does not satisfy high or low criteria)	HIGH (must satisfy at least 3)
≤4 joints throughout their disease course	• Persistent oligoarthritis • Psoriatic arthritis • Enthesitis-related arthritis • Undifferentiated arthritis	• Hip or cervical spine arthritis • Ankle or wrist arthritis & marked or prolonged increase in inflammatory markers • Erosions or joint space narrowing seen on x-ray	• ≤1 active joints • Normal ESR or CRP level • Physician (MD) global assessment[1] of overall disease activity <3 of 10 • Patient/ parent global assessment[2] of overall well-being <2 of 10	• ≥1 features more than low disease activity level & <3 features of high disease activity	• ≥2 active joints • ESR or CRP >2x upper limit of normal (ULN) • MD global assessment[1] of overall disease activity ≥7 of 10 • Patient/ parent global assessment[2] of overall well-being ≥4 of 10
≥5 joints throughout their disease course	• Extended oligoarthritis • RF-negative polyarthritis • RF-positive polyarthritis • Psoriatic arthritis • Enthesitis-related arthritis • Undifferentiated arthritis	• Hip or cervical spine arthritis • Positive RF or anti-CCP antibodies • Erosions or joint space narrowing seen on x-ray	• ≤4 active joints • Normal ESR or CRP level • MD global assessment[1] of overall disease activity <4 of 10 • Patient/ parent global assessment[2] of overall well-being <2 of 10	• ≥1 features more than low disease activity level & <3 features of high disease activity	• ≥8 active joints • ESR or CRP >2x ULN • MD global assessment[1] of overall disease activity ≥7 of 10 • Patient/ parent global assessment[2] of overall well-being ≥5 of 10

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[1]Physician's (MD) global assessment consists of rating the overall level of the child's disease activity based on a 10 cm visual analogue scale (VAS): 0=no activity; 10=maximum activity

[2]Parent's global assessment consists of their rating on the child's overall well-being based on a 10 cm VAS: 0=very good; 10=very poor

3 JIA TREATMENT GROUP (CONT'D)

JIA TREATMENT GROUP	JIA SUBTYPE	FEATURES OF POOR PROGNOSIS (must satisfy at least 1)	DISEASE ACTIVITY LEVELS		
			LOW (must satisfy all)	MODERATE (does not satisfy high or low criteria)	HIGH (must satisfy at least 3)
Active sacroiliac arthritis	• Psoriatic arthritis • Enthesitis-related arthritis • May be any of the JIA subtype	• Erosions or joint space narrowing seen on x-ray	• Normal back flexion • Normal ESR or CRP level • MD global assessment[1] of overall disease activity <4 of 10 • Patient/parent global assessment[2] of overall well-being <2 of 10	• ≥1 features more than low disease activity level & <2 features of high disease activity	• ESR or CRP >2x ULN • MD global assessment[1] of overall disease activity ≥7 of 10 • Patient/parent global assessment[2] of overall well-being ≥4 of 10
Systemic arthritis w/ active arthritis & without active systemic features	Systemic arthritis w/ active arthritis	• Hip arthritis • Erosions or joint space narrowing seen on x-ray	• ≤4 active joints • Normal ESR or CRP level • MD global assessment[1] of overall disease activity <4 of 10 • Patient/parent global assessment[2] of overall well-being <2 of 10	• ≥1 features more than low disease activity level & <3 features of high disease activity	• ≥8 active joints • ESR or CRP >2x ULN • MD global assessment[1] of overall disease activity ≥7 of 10 • Patient/parent global assessment[2] of overall well-being ≥5 of 10

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JIA TREATMENT GROUP	JIA SUBTYPE	FEATURES OF POOR PROGNOSIS (must satisfy at least 1)	DISEASE ACTIVITY LEVELS		
			LOW (must satisfy all)	MODERATE (does not satisfy high or low criteria)	HIGH (must satisfy at least 3)
Systemic arthritis w/ active systemic features & without active arthritis	Systemic arthritis w/ active fever of systemic JIA w/ or without other systemic features & without active arthritis	• 6 months duration of significant active systemic disease (ie fever, increased inflammatory markers, systemic corticosteroids required for the treatment)	• Active fever & MD global assessment[1] of overall disease activity <7 of 10 • Active fever & systemic features of high disease activity that result in MD global assessment[1] of overall disease activity ≥7 of 10		

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PRINCIPLES OF THERAPY

- Objectives in treating children w/ JIA
  - To achieve disease remission
  - To control pain
  - To preserve range of motion, muscle strength & function
  - To control systemic complications
  - To foster normal nutrition, growth, & physical & psychological development
- Management approach is customized based on the disease subtype & severity, occurrence of poor prognostic factors & response to treatment
- Tuberculosis (TB) infection should be ruled out prior to starting anti-TNF-α; testing for hepatitis B & C should be done prior to giving Methotrexate or anti-TNF-α in children w/ risk factors for infection
- Immunization status must be updated prior to receiving treatment
  - Live vaccines should not be given in patients given glucocorticoids or disease-modifying antirheumatic drugs (DMARDs)
  - Inactive vaccines are not contraindicated
  - Yearly immunization w/ influenza is recommended

A NON-PHARMACOLOGICAL THERAPY

Nutritional Therapy

- Calcium intake in children w/ JIA should be monitored & daily intake be increased
  - Patient's w/ JIA have been shown to have low bone mineral density (BMD) regardless of steroid use
  - Pathologic fractures have been noted in 15-26% of children w/ JIA
- Calcium plus vitamin D is advised in some patients especially those on corticosteroids
  - Corticosteroid causes bone loss which further increases the risk of osteoporosis & osteopenia
  - Steroids reduce calcium absorption & increase urinary calcium loss that leads to bone resorption
- Evaluate & ensure appropriate protein & caloric intake

Orthotics Management

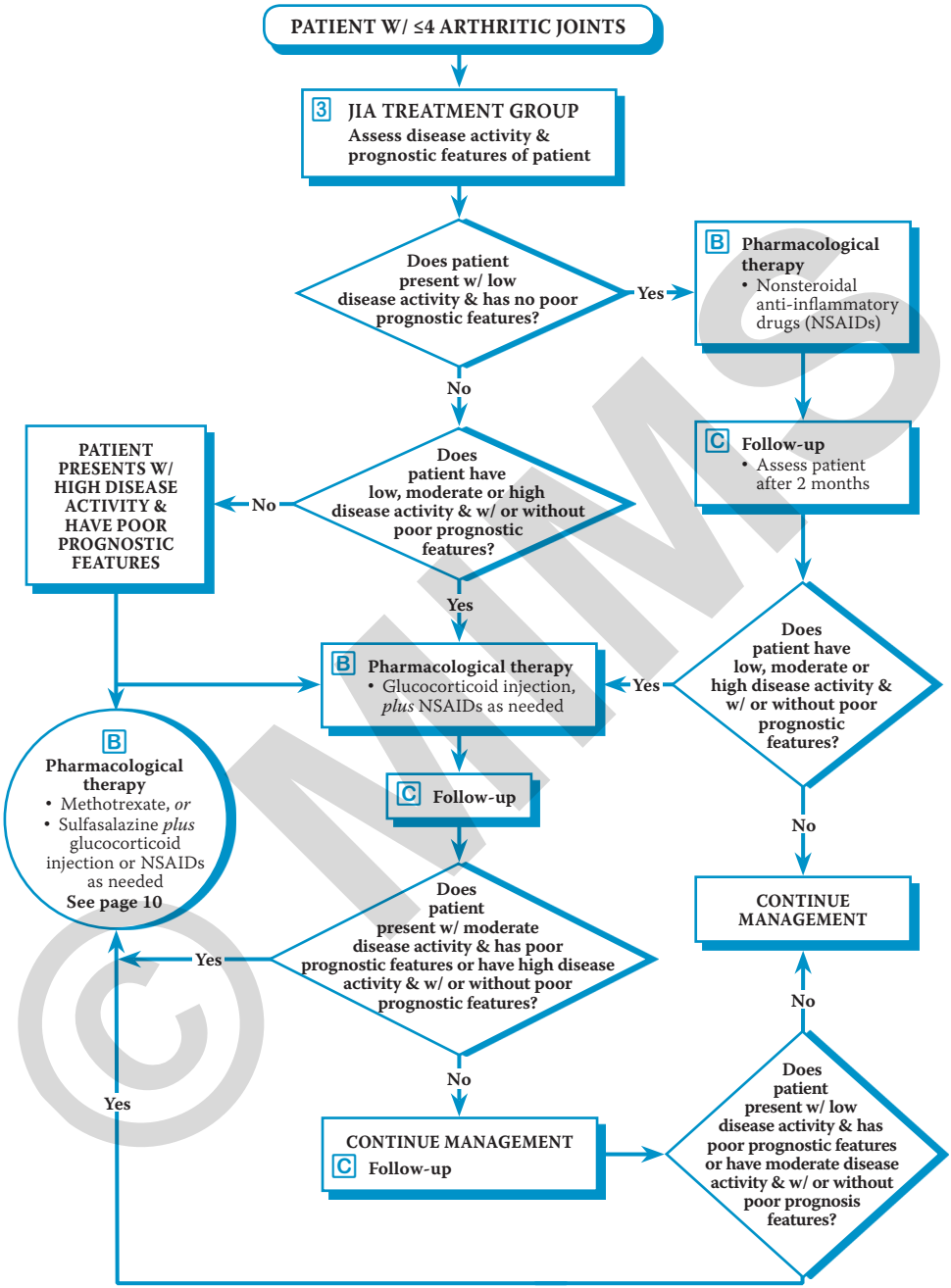
- Splints & foot orthotics may be recommended on an individualized basis
- Benefit of splints depends on the patient's age, type of orthosis used & the location of the joint affected
- Splints can be used as adjuncts to pharmacological therapy to increase range of movement & prevent contractures
- Help maintain function, maintain good joint position, relieve pain, stretch contracted joints & support inflamed joints

Physical Activity

- Provides important general health benefits & may improve disease outcomes without causing disease exacerbation
- Reduces loss of proteoglycans & cartilage damage, optimizes BMD, & decreases obesity risk that may worsen joint load
- Reduces the risk of osteopenia & osteoporosis
- A minimum of 6 weeks exercise program may provide:
  - Improved aerobic fitness
  - Better muscle strength & function
  - Lesser disease activity
  - Improved self-efficacy, energy level & quality of life
  - Decreased pain & use of medicines
- Aquatic exercises promote range of motion, strength & fitness w/ lower stress on joints
- Weight bearing exercise should be recommended to develop optimal bone width & density
- Moderate fitness & strengthening exercises are recommended for children w/ JIA
  - If patient has well controlled disease & have adequate physical activity, competitive or impact sports may be an option
  - Patients w/ moderate-severe impairment or active joint inflammation should be advised to limit activities within pain thresholds & then gradually return to full activity after disease exacerbation
- Children w/ neck arthritis should have x-ray screening for C1-C2 instability before joining any contact sports
- Use of appropriately fitted mouth guards & eye protection should be recommended during activities

Thermotherapy

- Heat &/or cold may be advised for relief of JIA symptoms
  - Heat treatments (eg heat packs, deep heat ultrasound, warm baths) may be helpful in lessening joint rigidity, pain & muscle spasms, & increasing joint flexibility
    - Morning warm bath or shower may help decrease stiffness & pain
  - Massage, which is often given w/ heat therapy, may help ease pain, reduce anxiety, promote relaxation, & prevent adhesions in subcutaneous tissues
  - Cold treatment (eg cold packs) causes vasoconstriction in joints w/ inflammation & may help in pain relief



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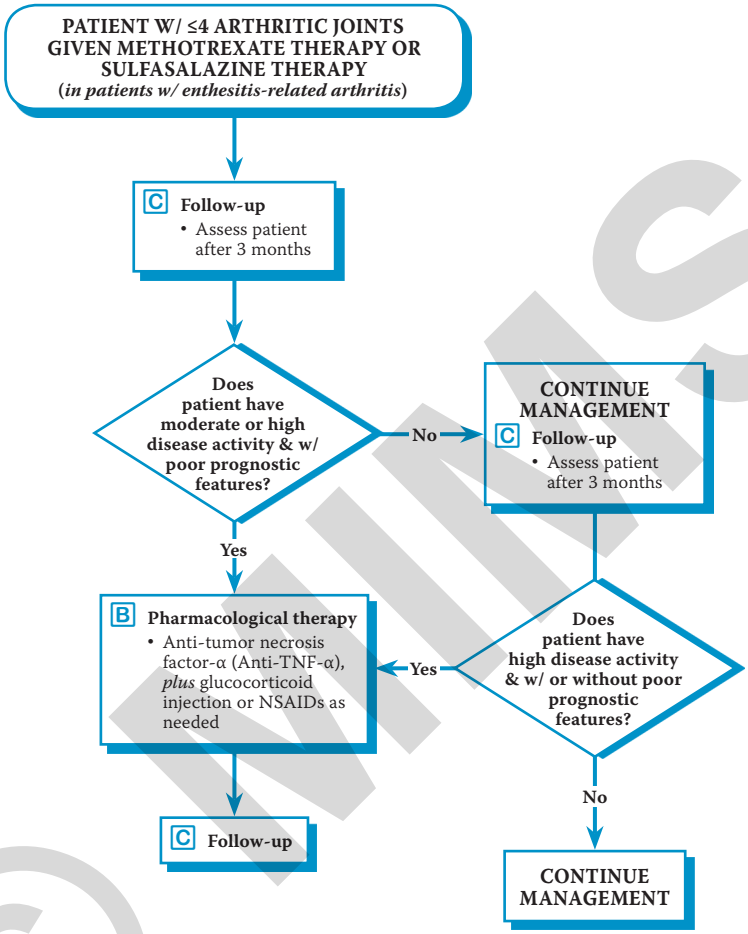

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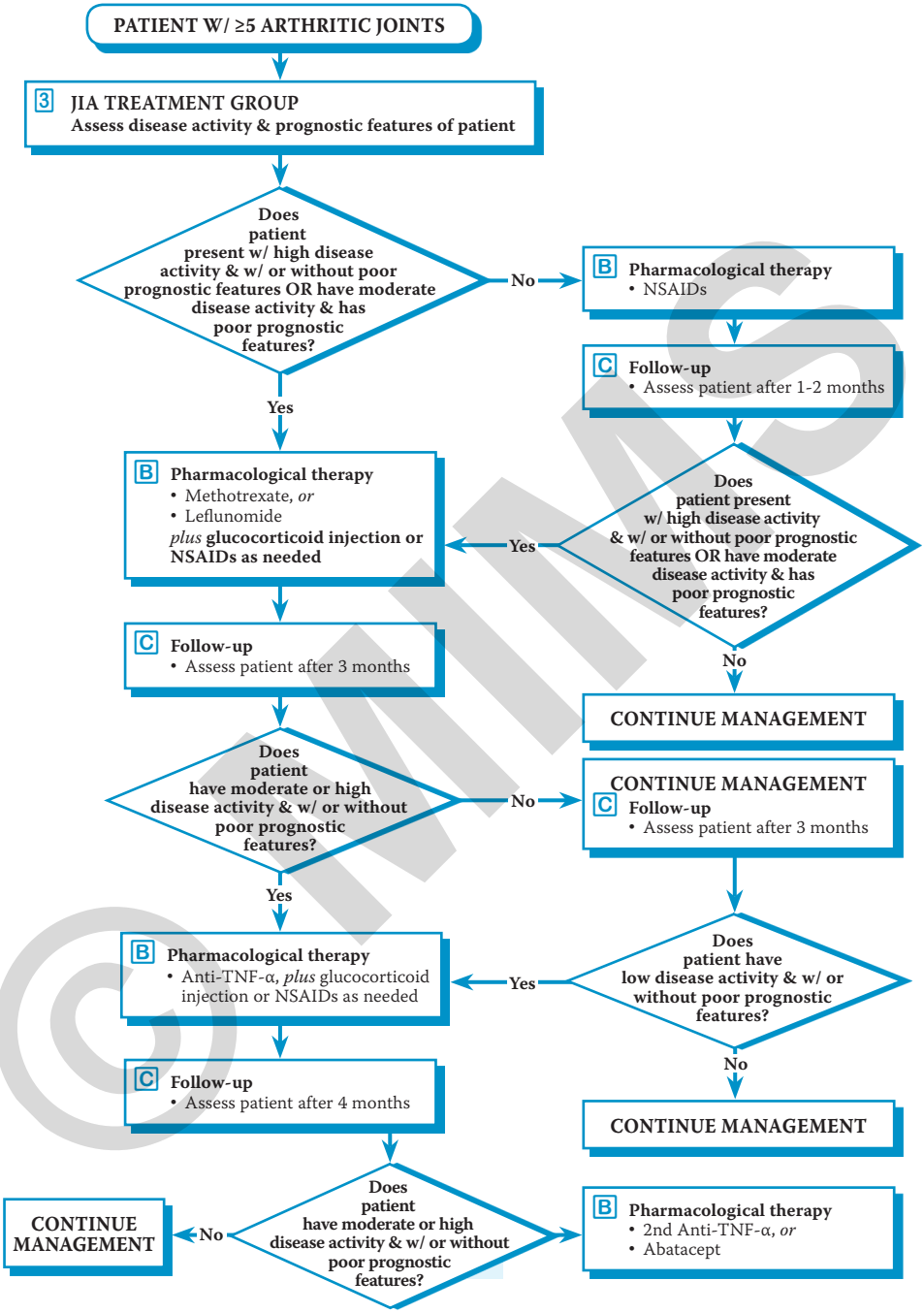

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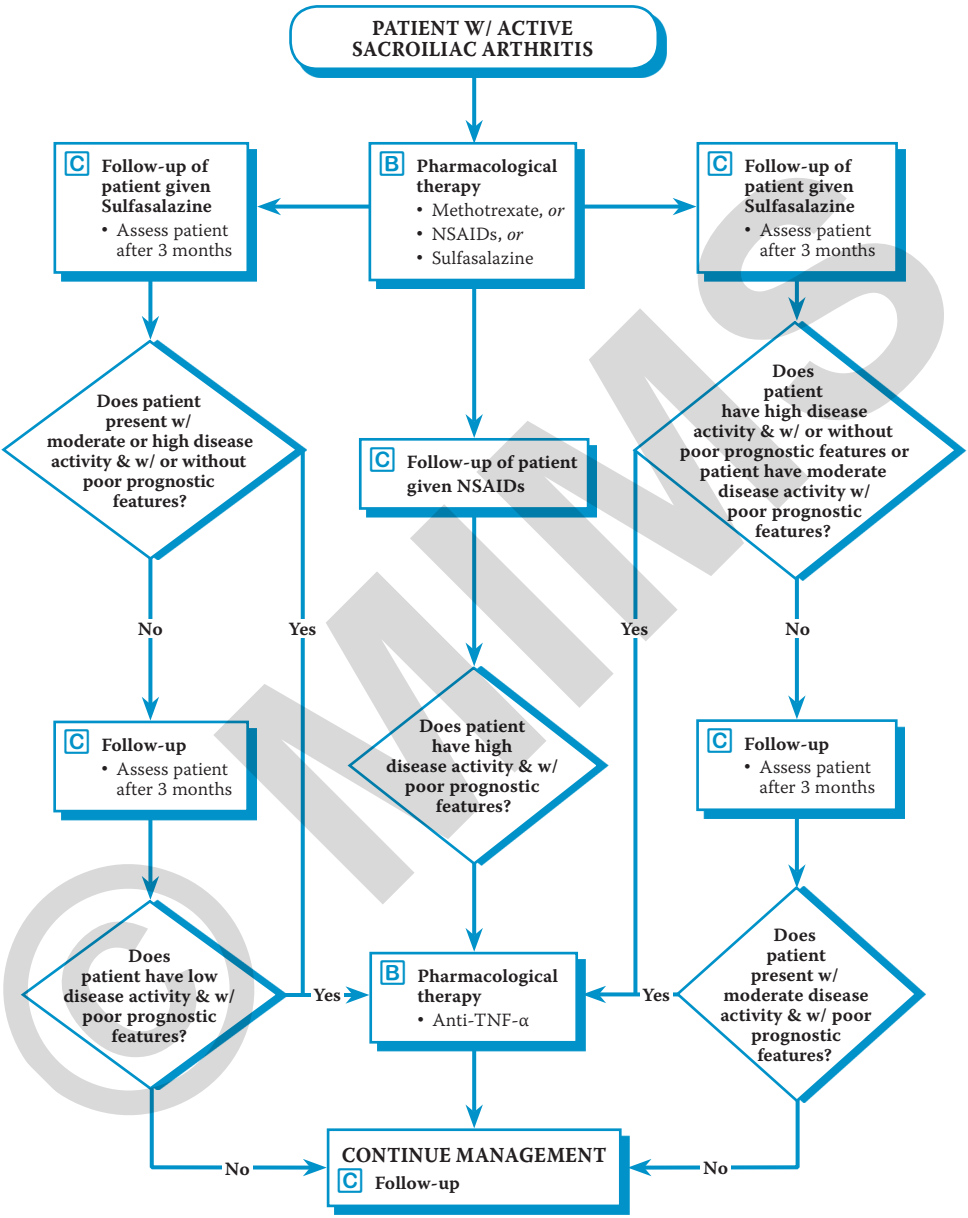

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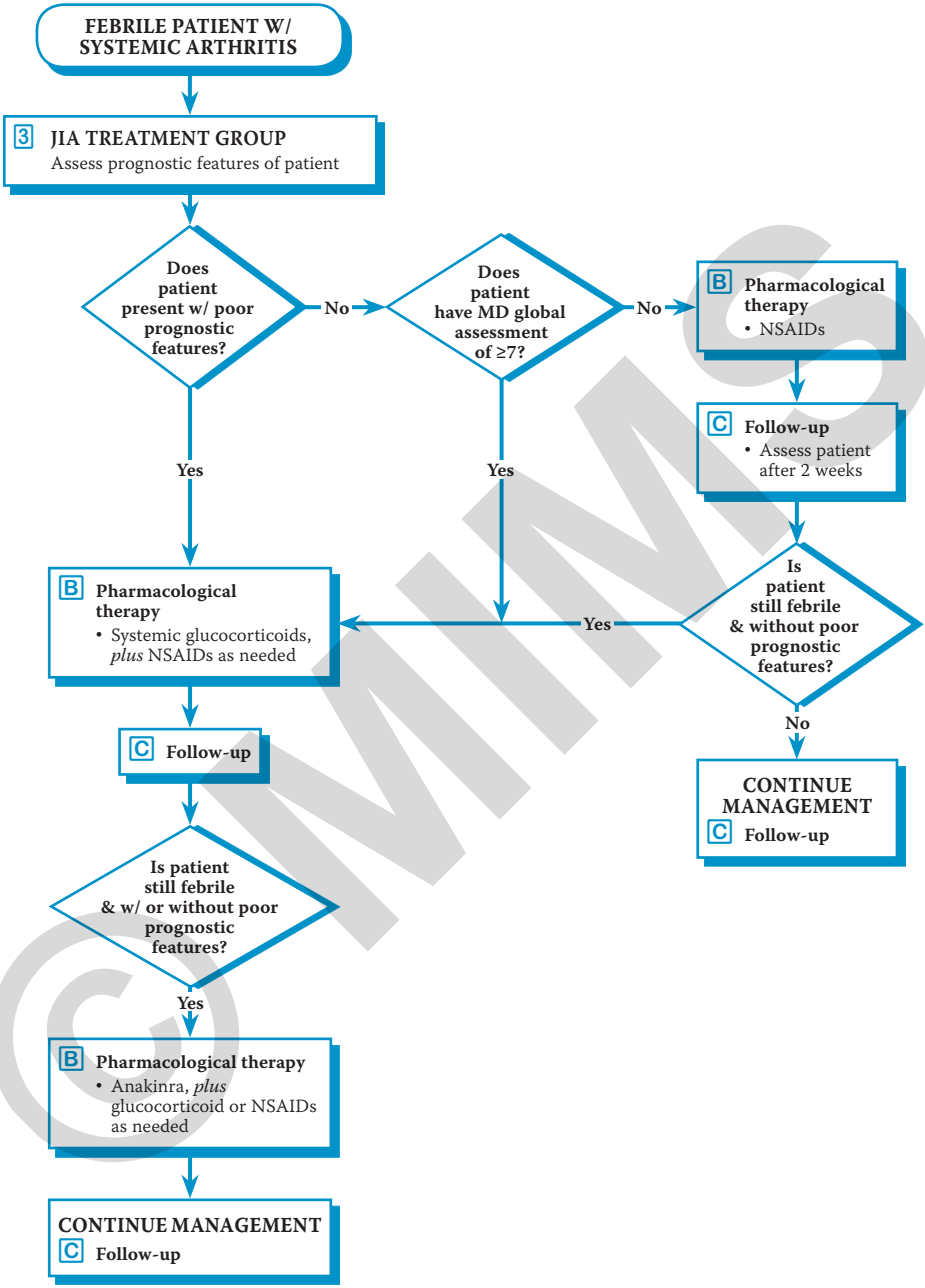

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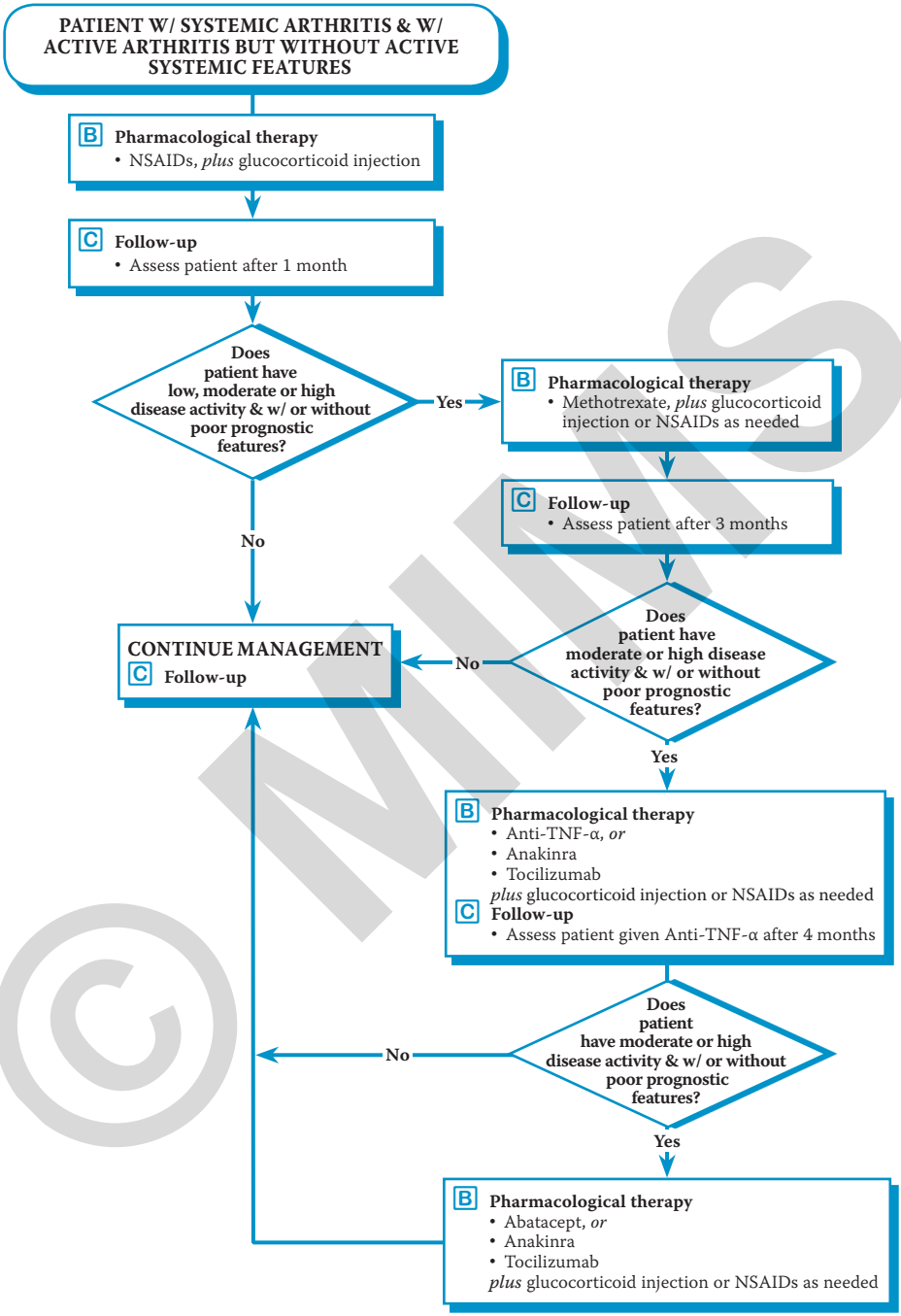

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B PHARMACOLOGICAL THERAPY

Analgesic

- Paracetamol may be considered for short-term use in treating persistent JIA pain in children & adolescents
- In addition to Paracetamol, Codeine may be given to manage moderate articular pain

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

- Considered the 1st-line drug for the treatment of inflammation & associated pain in children w/ JIA
  - Used for the initial management of pain, stiffness & inflammation
- Exert anti-inflammatory, analgesic & antipyretic effects w/ long-term safety when used appropriately
  - Anti-inflammatory effects in JIA patients is noted after 4-6 weeks of constant administration
- NSAID monotherapy is recommended for patients w/ low disease activity, w/ no joint contractures & features of poor prognosis, & during the clinical evaluation of possible systemic arthritis
  - Continued use without additional therapy for >2 months is discouraged in patients w/ active arthritis regardless of presence of poor prognostic features; continued use for >1 month in patients w/ active fever is not advised
- Patients w/ systemic arthritis w/ active arthritis & without active systemic features may be started on NSAID monotherapy w/ or without intraarticular corticosteroids if w/ low disease activity & without poor prognostic features
- Studies have shown that effectivity & tolerability of selective COX-2 inhibitors (eg Celecoxib, Meloxicam) are similar to the non-selective NSAIDs (eg Naproxen)
- Use of NSAIDs alone seldom induce remission of polyarticular or systemic-onset JIA

Corticosteroids

Intra-articular

- Use for joint injections in active arthritis is recommended regardless of disease activity level, prognostic features, joint contractures, concomitant therapy or JIA treatment group
- Triamcinolone hexacetonide is commonly used for joint injections due to its superior efficacy
  - Improvement of arthritis may be noted after at least 4 months of use & may be repeated as needed
  - Intensification w/ systemic therapy may be needed when patient improved clinically for only a short duration of time

Systemic

- Recommended as initial therapy for patients w/ systemic arthritis that have active fever & MD global assessment ≥7 but has no active arthritis
  - Started in patients w/ systemic arthritis that have active fever after 2 weeks of NSAID use
- Recommended for bridge therapy while waiting for the therapeutic response to a DMARD, for control of uveitis & for the management of severe systemic illness

Biologic Disease Modifying-Antirheumatic Drugs (DMARDs)

- Target specific cytokines (eg interleukin-1, interleukin-6) or interfere w/ specific cell function through depletion of B cells or suppression of T cell activation

Anti-tumor Necrosis Factor-α (Anti-TNF-α)

- Recommended in patients w/ ≤4 arthritic joints who have received glucocorticoid joint injections & 3 months of maximum tolerated dose of Methotrexate that have moderate or high disease activity & features of poor prognosis
  - Also given to patients who have received glucocorticoid joint injections & 6 months of Methotrexate that have high disease activity w/ no features of poor prognosis
  - Also recommended in patients w/ enthesitis-related arthritis who were given glucocorticoid joint injections & a trial of Sulfasalazine (without prior Methotrexate) & have moderate or high disease activity without considering the prognostic features
- In patients w/ ≥5 arthritic joints, anti-TNF-α is recommended in patients who have received the maximum tolerated dose of Methotrexate or Leflunomide for 3 months & have moderate or high disease activity regardless of prognostic features
  - Also used in patients w/ low disease activity who have received Methotrexate or Leflunomide for 6 months, irrespective of prognostic features
  - Changing from 1 anti-TNF-α to another may be advised in patients w/ moderate or high disease activity who have used the current anti-TNF-α for 4 months, regardless of poor prognostic factors
  - In patients who have received Abatacept for 3 months & have high disease activity w/ features of poor prognosis & in patients who have received Abatacept for 6 months & have moderate or high disease activity w/ or without features of poor prognosis, switching to anti-TNF-α is recommended

B PHARMACOLOGICAL THERAPY (CONT'D)

Biologic DMARDs (Cont'd)

Anti-TNF-α (Cont'd)

- Recommended more readily in patients w/ active sacroiliac arthritis
  - Given to patients w/ active sacroiliac arthritis who have received an adequate trial of NSAIDs & have high disease activity & poor prognostic features
  - Also recommended in patients who were maintained on Methotrexate for 3 months w/ high disease activity irrespective of prognostic factors, or w/ moderate disease activity w/ poor prognosis, or in patients given 6 months of Methotrexate w/ moderate disease activity w/ no poor prognostic features
  - Also given to patients w/ moderate or high disease activity who have used Sulfasalazine for 3 months, irrespective of prognostic features, or to patients w/ low disease activity & poor prognostic features who were on 6 months of Sulfasalazine
- In patients w/ systemic arthritis w/ active arthritis & without active systemic features, anti-TNF-α is recommended to be initiated or added if patient received Methotrexate for 3 months, w/ moderate or high disease activity w/ or without poor prognostic features
- When used up to the maximum recommended dosing regimen, may show response in 2-4 weeks in some patients
  - Usually cause significant improvement in symptoms, signs &/or lab parameters within 12-24 weeks
  - BMD was noted to improve after treatment w/ anti-TNF-α agents even in patients w/ incomplete disease control
- Adalimumab & Infliximab appear to be more effective in JIA-associated uveitis than Etanercept
  - Recommended for Methotrexate-resistant anterior uveitis
- Some studies indicate that anti-TNF-α dose may be decreased when patients are in remission or in low disease activity, without losing its efficacy
- Adalimumab
  - A fully human, IgG, monoclonal anti-TNF antibody
  - Approved to reduce signs & symptoms of moderate-severe active polyarthritis in patients ≥4 years old
  - Treatment option for children ≥2 years old & w/ inadequate response to ≥1 DMARD
  - May be used alone or in combination w/ Methotrexate
- Etanercept
  - Soluble TNF p75 receptor fusion protein that binds to & inactivates TNF-α
  - First anti-TNF-α to be approved for use in JIA
  - A standard therapy given to patients w/ arthritis that did not respond to Methotrexate
  - May be used in children as young as 2 years old for treating moderate-severe polyarticular JIA
  - Shown to be less effective in patients w/ systemic-onset JIA than in patients w/ other forms of JIA
  - Should not be given to children w/ infection or history of recurrent infections
  - Can be used continuously for up to 8 years, as indicated by its long-term safety profile
    - Exacerbation & worsening of the disease are the 2 most common serious adverse effects noted beyond 4 years of use
- Infliximab
  - A chimeric human/mouse monoclonal antibody that binds to soluble & membrane-bound TNF-α
  - Use in JIA needs further study because of its potential adverse effects (eg infusion reactions, development of antibodies)
- Golimumab
  - A fully human, IgG, monoclonal anti-TNF antibody that can be administered either intravenously or subcutaneously
  - One study showed subcutaneous Golimumab led to quick & clinically relevant improvement
  - Not approved by the US FDA for treatment of JIA but IV dosing for JIA is under investigation

Anti-Cytotoxic T Lymphocyte–Associated Antigen-4 Immunoglobulin

- Abatacept
  - A fully human, soluble fusion protein that contains the extracellular domain of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) & the Fc component of IgG1
  - Selectively inhibits the costimulatory signal needed for T-cell activation
  - Approved for the management of patients w/ moderate-severe polyarticular JIA
    - In combination w/ Methotrexate is indicated for patients ≥6 years old w/ moderate to severe active polyarticular JIA & had inadequate response to other DMARDs including ≥1 TNF inhibitor

B PHARMACOLOGICAL THERAPY (CONT'D)

- Abatacept (Cont'd)
  - Recommended as an alternative management in patients w/ ≥5 arthritic joints who were maintained for 4 months on anti-TNF-α & have high disease activity, irrespective of poor prognostic features, or moderate disease activity w/ poor prognostic features
  - Also advised as another treatment approach in patients given ≥1 consecutive anti-TNF-α & have moderate or high disease activity, irrespective of prognostic factors, or low disease activity w/ poor prognostic features
  - Given to patients w/ systemic arthritis that has no active systemic features, who have received Methotrexate & anti-TNF-α & w/ high disease activity, regardless of prognostic features, or patients w/ moderate disease activity & features of poor prognosis
  - May be as effective as anti-TNF-α agents as shown by different studies; however, maximum efficacy was noted a few weeks later

Anti-CD20

- Rituximab
  - A chimeric monoclonal antibody to CD20 that causes selective depletion of CD20-positive B cells which may produce anti-inflammatory effects in arthritis
  - Recommended as an alternative treatment option in patients w/ ≥5 arthritic joints who have received anti-TNF-α & Abatacept consecutively & have high disease activity, without considering the prognostic features, or in patients w/ moderate disease activity w/ poor prognostic features
    - More appropriate to use in patients w/ positive RF

Interleukin-1 Receptor Antagonist

- Anakinra
  - A recombinant human interleukin-1 receptor antagonist
  - Recommended in all patients w/ systemic arthritis that has active fever & features of poor prognosis, regardless of current therapy
  - Also given to all patients w/ systemic arthritis that develops or continue to have fever while receiving systemic glucocorticoids
  - May be added or started in patients w/ systemic arthritis but has inactive systemic features, after receiving Methotrexate & have moderate or high disease activity, irrespective of poor prognostic features
  - Also advised in patients w/ high or moderate disease activity who have received Methotrexate & anti-TNF-α or Methotrexate & Abatacept, regardless of prognostic factors
  - In patients w/ systemic arthritis but w/ inactive systemic features, initiation of Anakinra may be less appropriate later in the disease course than near the disease onset
  - May be switched to anti-TNF-α agents in patients w/ moderate or high disease activity, irrespective of poor prognostic features; however unmasking of latent systemic disease activity is possible when Anakinra is discontinued
- Canakinumab
  - A recombinant human monoclonal interleukin-1β antibody
  - Recommended as an alternative treatment for >2 years old patients w/ systemic arthritis w/ active systemic features & w/ continued disease activity despite therapy w/ glucocorticoids, Methotrexate & other first-line drugs
  - Also recommended as an alternative treatment option in patients w/ systemic arthritis without active systemic features & w/ >4 arthritic joints after receiving DMARD combined w/ Anakinra, Tocilizumab, Abatacept, or an anti-TNF-α agent
- Rilonacept
  - A fusion protein w/ human cytokine receptor extracellular domains for both IL-1 type 1 receptor & IL-1 accessory protein
  - Further studies are needed to prove the efficacy of Rilonacept in JIA patients
    - Studies have shown uncertain/inappropriate effects of Rilonacept in patients w/ systemic arthritis w/ or without systemic features

Interleukin-6 Receptor Antagonist

- Tocilizumab
  - A humanized monoclonal antibody that inhibits the cytokine IL-6
  - Recommended for children & adolescents ≥2 years old w/ active systemic JIA who had responded inadequately to NSAIDs, systemic corticosteroids & Methotrexate
  - May also be given to children & adolescents ≥2 years old w/ refractory systemic onset of JIA & polyarticular JIA

B PHARMACOLOGICAL THERAPY (CONT'D)

Non-Biologic DMARDs

Methotrexate

- Recommended as the initial therapy for patients w/ ≤4 arthritic joints that have high disease activity & features of poor prognosis
  - Also given to patients w/ high disease activity without features of poor prognosis & to patients w/ moderate disease activity w/ features of poor prognosis after initial glucocorticoid injection
  - After repeated glucocorticoid injections, Methotrexate may be started in patients w/ moderate disease activity without features of poor prognosis or in patients w/ low disease activity w/ features of poor prognosis
- In patients w/ ≥5 arthritic joints, Methotrexate may be given as initial treatment for patients w/ high disease activity regardless of poor prognostic factors & for patients w/ moderate disease activity & features of poor prognosis
  - After 1 month of NSAID use, Methotrexate may be started in patients w/ low disease activity & features of poor prognosis or in patients w/ moderate disease activity without features of poor prognosis if NSAID was used for 1-2 months
- Recommended for patients w/ systemic active arthritis but w/ no active systemic features after ≤1 month of NSAID use irrespective of poor prognostic features
  - Not appropriate for initial treatment of patients w/ active fever & without active arthritis
- Effective at relatively low oral dose, has relatively fast onset of action & acceptable toxicity (ie absence of risk for oncogenicity & production of sterility)
- Response is usually observed after ≥3 months of use & is advised to be continued for ≥1 year after achieving remission
- May be continued while starting anti-TNF-α (ie Etanercept, Adalimumab) in patients who had partial clinical response to previously given Methotrexate
- Folic acid at 1mg/day should be given concomitantly to decrease gastrointestinal irritation & mucosal toxicity without decreasing Methotrexate's effectivity
- Adolescents taking Methotrexate should be advised to avoid alcohol, smoking & pregnancy

Hydroxychloroquine

- Used as additional drug to treat chronic arthritis in older children
  - Usually added to NSAID regimen; rarely given as monotherapy
- Therapeutic response is rarely seen before 2-3 months of therapy; should be discontinued if no improvement after 6 months of use
- Eye exam (ie test of color vision & visual fields) should be performed before therapy
- Not recommended for children <4 years old

Leflunomide

- May be used as an alternative to Methotrexate
- One of the treatment options for patients w/ ≥5 arthritic joints that have high disease activity & features of poor prognosis
  - May also be given as initial treatment for patients w/ high disease activity w/ no poor prognostic features & for patients w/ moderate disease activity w/ poor prognostic features after a brief trial of NSAIDs
- Therapeutic effects may be noted 4 weeks after starting the therapy & continues until 5 months of treatment
- Studies have shown cases of severe liver injury in rheumatoid arthritis patients who used Leflunomide

Sulfasalazine

- Recommended for patients w/ enthesitis-related arthritis w/ moderate or high disease activity after glucocorticoid joint injection or NSAID use, regardless of features of poor prognosis
- Effects are noted within 4-8 weeks after starting the therapy
- Generally not advisable to children w/ active systemic JIA due to increased hypersensitivity reactions

C FOLLOW-UP

- Patients are considered to have inactive disease if they have no active synovitis, fever, rash, serositis, splenomegaly, generalized lymphadenopathy, or active uveitis, have normal ESR &/or CRP, & the physician's global assessment indicates no active disease
  - Patient on medication who have inactive disease for 6 consecutive months is considered to have clinical remission on medication
  - Patients not taking any anti-arthritis or anti-uveitis medication & have inactive disease for 12 continuous months are considered to have clinical remission
- Ten year remission rate in 50% of patients w/ oligoarthritis is noted; 40% in patients w/ systemic arthritis & 15% in patients w/ polyarthritis
  - Long-term remission in patients w/ RF-positive polyarthritis is unlikely
- Follow up of patients depend on the disease severity & medications given; may be every 2 weeks-3 months
- Activity of arthritis should be evaluated at least 3x/year & treatment be adjusted to reduce joint swelling & tenderness
- Should identify complications of JIA such as macrophage activation syndrome (MAS)
  - An uncommon but potentially fatal complication of systemic-onset JIA
    - Febrile patients who are diagnosed or suspected to have JIA are considered to have MAS if laboratory results show a ferritin level of >684 ng/mL & any 2 of the following: Platelet count ≤181 x 10^9/L, aspartate aminotransferase >48 U/L, triglycerides >156 mg/dL & fibrinogen ≤360 mg/dL.
  - Patient may also present w/ acute onset of severe anemia coupled w/ thrombocytopenia or leukopenia that have high spiking fevers, lymphadenopathy, & splenomegaly
  - May be differentiated from patients w/ exacerbation of systemic disease through fall of ESR secondary to hypofibrinoginemia & hepatic dysfunction
  - Diagnosis is confirmed by hemophagocytosis seen in bone marrow biopsy
    - Presence of which may not always be evident, especially in the early stages of the disease
  - High-dose IV Methylprednisone, Cyclosporine, or Anakinra may be effective emergency treatment
- Screening of comorbidities should also be done
  - TB testing should be repeated at least once every year in all patients maintained on anti-TNF-α agents
  - Patients who are female, <6 years old at JIA onset, w/ oligoarthritis subtype, w/ <4 years duration, w/ positive ANA & negative RF are considered at high risk to develop uveitis & should be screened every 3-4 months
    - Patients w/ medium risk (ie oligoarthritis or polyarthritis, ≥6 years old at onset, w/ negative ANA) should be screened every 6 months, & yearly for those at low risk (ie systemic-onset JIA)
- Screening for uveitis associated w/ JIA should be done regularly & treatment should be initiated based on current evidenced-based guidelines to prevent complications & to preserve vision
  - Screening should be done within 6 weeks in newly diagnosed patients w/ JIA
- Safety of treatment given should be regularly assessed
  - Monitoring for NSAID use
    - Serum crea, CBC & LFT should be measured prior to or soon after the initiation of treatment
    - Serum crea, urinalysis, CBC & LFT should be checked 2x/year in patients maintained on long-term daily NSAIDs & yearly for patients taking NSAIDs routinely
  - Monitoring for Methotrexate use
    - Serum crea, CBC & LFT should be measured prior to, 1 month after the initiation of treatment & 1-2 months after a dose escalation
    - 3-4 monthly measurement of serum crea, CBC & LFT should be recommended in patients receiving stable dose of Methotrexate w/ no recent history of abnormal lab results
    - Lab tests should be done 1-2 days before the scheduled weekly dose of Methotrexate
    - For abnormal LFT results, the following are recommended:
      - LFT 2x ULN: No specific action or recheck LFT at shorter interval
      - LFT >2x ULN: Reduce dose or temporarily stop the medication
      - LFT >3x ULN even after decreasing the dose: Discontinue use
  - Monitoring for anti-TNF-α use
    - If drug will be used continuously, serum crea, CBC & LFT should be tested prior to therapy & every 3-6 months thereafter
- For patients who fail to have disease control w/ any of the medications, autologous stem cell transplantation may be an option to achieve disease remission, but is still currently being evaluated

Dosage Guidelines

ANALGESIC (NON-OPIOIDS)

Drug	Dosage	Remarks
Salicylic Acid & Derivatives		
Aspirin (Acetylsal acid/Acetylsalicylic acid)	80-100 mg/kg PO daily in 5-6 divided doses **Max dose:** 130 mg/kg/day	**Adverse Reactions** • GI effects (N/V, dyspepsia, ulceration, hematemesis); Hematologic effects (iron deficiency anemia after long-term use, hypoprothrombinemia); Dermatologic effects (urticaria, angioedema); Hypersensitivity reactions (bronchospasm, dyspnea); Other effect (hepatotoxicity) • Salicylism (dizziness, tinnitus, deafness, sweating, N/V, headache, confusion) may occur after repeated use of large doses **Special Instructions** • May be given w/ food to decrease GI effects • Avoid use in patients w/ hemophilia or other hemorrhagic disorders, history of allergy to other NSAIDs, severe renal or hepatic impairment • Used w/ caution in patients prone to dyspepsia, w/ gastric ulcer, asthma or allergic disorders, renal or hepatic impairment, dehydration, G6PD deficiency, DM • Aspirin should be stopped several days prior to scheduled surgery

CORTICOSTEROIDS (INTRA-ARTICULAR)

Drug	Dosage	Remarks
Methylprednisolone (Methylprednisolone acetate)	**Small joints:** 4-10 mg/dose IA **Medium joints:** 10-40 mg/dose IA **Large joints:** 20-80 mg/dose IA	**Adverse Reactions** • Local effects (post-injection flare, thrombophlebitis, sterile abscess) **Special Instructions** • Systemic absorption should always be considered • Use w/ caution in patients w/ preexisting psychiatric conditions, heart failure, DM, GI diseases, hepatic impairment including cirrhosis, myasthenia gravis, renal impairment, history of seizure disorder, thyroid disease
Methylprednisolone (Methylprednisolone Na succinate)	0.11-1.6 mg/kg/day IV ***or*** IM divided 6-8 hrly **Pulse therapy:** 30 mg/kg/dose IV daily for 1-5 days **Max dose:** 1 g	
Triamcinolone (Triamcinolone acetonide, Triamcinolone hexacetonide)	**Childn 1-18 yr:** **Small joints:** 500 mcg/kg IA **Max dose:** 20 mg IA for small joints; 10 mg for finger & toe joints **Larger joints:** 1 mg/kg IA **Max dose:** 40 mg	

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Dosage Guidelines

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

Drug	Dosage	Remarks
Biological DMARDs		
Abatacept	**Childn 6-17 yr:** **<60 kg:** 500 mg **≥60-100 kg:** 750 mg **>100 kg:** 1000 mg *All doses should be administered as IV infusion & given at 2 & 4 wk after the 1st infusion & every 4 wk thereafter*	**Adverse Reactions** • Infusion related: Dizziness, headache, hypertension, rash, fever, flushing, chills; severe reactions eg anaphylaxis, convulsions & hypotension have occurred • Infections: Respiratory tract infections, urinary tract infections (UTIs), pneumonia, cellulitis, diverticulitis, acute pyelonephritis • Malignancies: lung cancer, lymphoma • Other effects: Depression, insomnia, GI effects (N/V, abdominal pain, dyspepsia); Rarely hepatotoxicity, optic neuritis, blood dyscrasias **Special Instructions** • Contraindicated in patients w/ moderate-severe CHF, patients w/ hypersensitivity to murine proteins • Use w/ caution in patients w/ chronic infection or history of recurrent infection; Do not administer >5 mg/kg dose in patients w/ CHF & use w/ caution in patients w/ mild CHF; Use w/ caution in patients w/ preexisting or recent onset of CNS demyelinating diseases or seizure disorders • Patient should be monitored for signs & symptoms of infections while on & after treatment; discontinue therapy if serious infection develops
Adalimumab	**Childn 4-17 yr:** **15 to <30 kg:** 20 mg SC every other wk **≥30 kg:** 40 mg SC every other wk	
Canakinumab	**sJIA:** **Childn ≥7.5 kg:** 4 mg/kg SC inj every 4 wk **Max dose:** 300 mg	
Etanercept	**Childn 4-17 yr:** 0.4 mg/kg SC 2x wkly given w/ 3-4 days interval **Max dose:** 25 mg/dose	
Golimumab	**Childn ≥40 kg:** 50 mg SC once mthly (same date each mth)	
Tocilizumab	**Children >2 yrs:** **≥30 kg:** 8 mg/kg IV infusion once every 2 wks <**30 kg:** 12 mg/kg IV infusion once every 2 wks	**Adverse Reactions** • CV effects (hypertension, edema); Dermatologic effects (pruritus, urticaria); CNS effects (headache, dizziness); GI effects (abdominal discomfort, stomatitis, weight gain); Other effects (neutropenia, thrombocytopenia, increased triglycerides, elevated LFT, infusion-related reactions) • One case of fatal anaphylaxis has been reported • Serious & potentially fatal infections (eg bacterial, mycobacterial, viral, fungal infections) have been reported - Reports of TB both reactivation of latent infection & new infection have been noted **Special Instructions** • Not recommended for patients w/ hepatic impairment • Use w/ caution in patients w/ demyelinating CNS disorders or w/ risk of GI perforation • Latent TB screening is recommended prior to treatment

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Dosage Guidelines

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs) (CONT'D)

Drug	Dosage	Remarks
Non-biological DMARDs		
Hydroxy-chloroquine	6.5 mg/kg/day PO **or** 400 mg/day PO, whichever is lower	**Adverse Reactions** • CNS effects (dizziness, headache, nervousness, seizure, vertigo); Dermatologic effects (alopecia, rash); GI effects (N/V, abdominal pain); Other effects (visual symptoms, muscle weakness) **Special Instructions** • Use w/ caution in patients w/ hepatic or renal impairment, G6PD deficiency, psoriasis, porphyria • Perform baseline ophthalmologic exam & every 3 mth • Test periodically for muscle weakness • Baseline assessment of hepatic & renal function is recommended
Leflunomide	**<40 kg:** 10 mg PO 24 hrly **>40 kg:** 20 mg PO 24 hrly	**Adverse Reactions** • GI effect (diarrhea); Hematologic effect (leukopenia); CNS effects (headache, dizziness, paresthesia); Musculoskeletal effects (joint disorder, synovitis); Other effects (eczema, alopecia, dry skin, weight loss, hypertension) **Special Instructions** • Contraindicated in immunocompromised patients, patients w/ severe infections, hepatic impairment, moderate-severe renal impairment, severe hypoproteinemia & bone marrow dysplasia • Use w/ caution in patients w/ history of TB & concurrent vaccination w/ live vaccines • Monitor CBC & BP regularly
Methotrexate	**Childn 1 mth-18 yr:** **Initial dose:** 10-15 mg/m^2 PO/ SC/IM once wkly **Max dose:** 25 mg/m^2 once wkly	**Adverse Reactions** • CNS effects (dizziness, fever, seizure); GI effects (N/V, loss of appetite, abdominal pain, diarrhea); Hematologic effects (anemia, leukopenia, thrombocytopenia), Other effects (alopecia, potentially fatal dermatologic reactions eg toxic epidermal necrolysis & Stevens-Johnson syndrome, impairment of fertility, oligospermia) • Low-dose Methotrexate has been associated w/ development of malignant lymphomas • Use may predispose patients to opportunistic infection **Special Instructions** • Contraindicated in patients w/ preexisting blood dyscrasias • Use w/ caution in patients w/ peptic ulcer disease, ulcerative colitis, renal impairment • May cause folic acid deficiency, consider giving folate supplementation at 1-5 mg/day • Monitor CBC w/ platelets, serum creatinine & LFT
Sulfasalazine	**Childn >6 yr:** 30-50 mg/kg/day PO divided 12 hrly **Max dose:** 2 g/day	**Adverse Reactions** • Hematologic effect (blood dyscrasia); GU effects (crystalluria, reversible oligospermia, renal toxicity); GI effects (anorexia, vomiting, diarrhea, abdominal pain); Other effects (headache, photosensitivity, body fluid discoloration, alopecia, hypersensitivity reactions, hepatotoxicity, fibrosing alveolitis) **Special Instructions** • Contraindicated in patients w/ hypersensitivity to sulfonamides or salicylates, intestinal or urinary obstruction, blood dyscrasias, history of leukopenia w/ gold therapy • Use w/ caution in patients w/ hepatic or renal dysfunction, G6PD deficiency, allergic bronchial asthma

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Dosage Guidelines

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Drug	Dosage	Remarks
Acetic Acid Derivatives		
Diclofenac	**Childn 6 mth-18 yrs:** 3-5 mg/kg/day PO in 2-3 divided doses **Max dose:** 150 mg/day	**Adverse Reactions** • GI effects (nausea, GI discomfort, diarrhea, peptic ulceration, GI bleeding); CNS effects (headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, insomnia); Hypersensitivity reactions (angioedema, bronchospasm, rashes, Stevens-Johnson syndrome occur rarely); Hematologic effects (anemia, thrombocytopenia, neutropenia); Other effects (hepatotoxicity, nephrotoxicity, hematuria, fluid retention, photosensitivity, pancreatitis) • Coxibs have lesser GI effects **Special Instructions** • May be given w/ food to decrease GI effects • Avoid use in patients w/ active peptic ulceration, severe heart failure, history of allergy to Aspirin or other NSAIDs - Coxibs should not be used in patients w/ moderate heart failure, ischemic heart disease, peripheral arterial disease, cerebrovascular disease • Use w/ caution in patients w/ infections, asthma or allergic disorders, hemorrhagic disorders, hepatic or renal impairment - Coxibs should be used w/ caution in patients w/ left ventricular failure, edema, history of cardiac failure, w/ risk factors for developing heart disease
Indomethacin	**Childn ≥2 yr:** 1-2 mg/kg/day PO divided 6-12 hrly **Max dose:** 200 mg daily **or** 4 mg/kg/day, whichever is lower	
Sulindac	**Childn >2 yr:** 4.5-6 mg/kg/day PO divided 12 hrly **Max dose:** 6 mg/kg day	
Tolmetin	**Childn >2 yr:** **Initial dose:** 20 mg/kg PO daily divided 6-8 hrly **Maintenance dose:** 15-30 mg/kg/day divided 6-8 hrly **Max dose:** 30 mg/kg/day	
Coxib		
Celecoxib	**≥10-≤25 kg:** 50 mg PO 12 hrly **>25 kg:** 100 mg PO 12 hrly	
Fenamic Acid Derivative		
Mefenamic	**Childn >6 mth**: 25 mg/kg/day in divided doses	
Oxicam Derivatives		
Meloxicam	0.125 mg/kg/day PO **Max dose:** 7.5 mg/day	
Piroxicam	**<15 kg:** 5 mg/day PO **16-25 kg:** 10 mg/day PO **26-45 kg:** 15 mg/day PO **≥46 kg:** 20 mg/day PO ***or*** **1st 2 days of serious pain:** 40 mg/day IM inj **Long-term therapy:** 10-20 mg/day	
Propionic Acid Derivatives		
Ibuprofen	20 mg/kg/day PO in divided doses **Max dose:** 40 mg/kg/day PO 6-8 hrly	
Naproxen	**Childn ≥2 yr:** 10 mg/kg PO daily divided 12 hrly **Max dose:** 15 mg/kg/day	

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