State of Palestine
Ministry of Health

Rheumatoid Arthritis Management Protocol

March 2014

Palestinian Ministry of Health

General Administration of pharmacy

Drug Information Department

Rheumatoid Arthritis Management Protocol

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Rheumatoid Arthritis Definition And Diagnosis

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves joints. An external trigger (eg, cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.

The arthritis is *symmetrical*, may be remitting, but if uncontrolled may lead to destruction of joints due to erosion of cartilage and bone which leads to deformity. The disease usually progresses from the periphery to more proximal joints, and in patients who do not fully respond to treatment, results in significant locomotor disability within 10 to 20 years.

The cause of RA is unknown. Genetic, environmental, hormonal , immunologic , and infectious factors may play significant roles. Socioeconomic, psychological, and lifestyle factors (eg, tobacco use, the main environmental risk may influence disease outcome. First-degree relatives of individuals with RA are at 2- to 3-fold higher risk for the disease. Women are affected by RA approximately 3 times more often than men are, but sex differences diminish in older age groups.

The 2010 ACR (College of Rheumatology) -EULAR (European League Against Rheumatism) Classification Criteria For Rheumatoid Arthritis: a score-based algorithm: add score of categories A-D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA

Target population: Patients who

1. have at least 1 joint with definite clinical synovitis (swelling)
2. with the synovitis not better explained by another disease

	Score
Joint involvement: refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal IP joints, first CMC joints, and first MTP joints are excluded from assessment.	
1 large joint (shoulders, elbows, hips, knees, and ankles)	**0**
2-10 large joints	**1**
1-3 small joints (MCP, proximal IP, second through fifth MTP joints, thumb IP joints, wrists) with or without involvement of large joints	**2**
4-10 small joints with or without involvement of large joints	**3**
>10 joints (at least 1 small joint) the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).	**5**
B. Serology (at least 1 test result is needed for classification)	
Negative RF (rheumatoid factor) *and* negative ACPA (anti-citrullinated protein antibody)	**0**
Low-positive RF or low-positive ACPA(IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay)	**2**
High-positive RF or high-positive ACPA (IU values that are >3 times ULN for laboratory and assay)	**3**
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP (C-reactive protein *)* and normal ESR (erythrocyte sedimentation rate)	**0**
Abnormal CRP or abnormal ESR	**1**
D. Duration of symptoms: patient self-report of duration of signs or symptoms of synovitis of joints that are clinically involved at time of assessment, regardless of treatment status.	
<6 weeks	**0**
≥6 weeks	**1**

Treatment

Goal of treatment is to control a patient's signs and symptoms, to prevent joint damage, and to maintain the patient's quality of life and ability to function. It is recommended that low disease activity or remission should be targeted for all patients with early or established disease who are receiving a DMARD or a biologic agent.

Nonpharmacologic treatment: patient education and counseling, rest, exercise, physical and occupational therapy, nutrition and dietary therapy, bone protection, atherosclerosis risk factor modification, nutritional supplements (calcium, vitamin d, fish oil), CV risk reduction (smoking cessation, lipid lowering)

Pharmacologic therapy:

1. *Analgesics* and *Nonsteroidal antiinflammatory drugs*
2. *Glucocorticoids*
3. *Disease-modifying antirheumatic drugs* (DMARDs)
   - Nonbiologic DMARDs : hydroxychloroquine, MXT , leflunomide.
   - Biologic DMARDs: Tumor necrosis factor alpha inhibitors: etanercept, adalimumab, rituximab.
   - Combination therapy of nonbiologic and biologics DMARDs

Recommended screening prior to starting, resuming, or significantly increasing therapy with nonbiologic or biologic DMARDs includes:

- Complete blood count and serum creatinine and aminotransferases
- Prior to MXT , or biologic DMARDs: Screening for hepatitis B and C
- Hydroxychloroquine : complete baseline ophthalmologic exam within first year of treatment,
- Testing for latent TB prior to all biologic DMARDs

Early rheumatoid arthritis: disease manifestations that have been present for less than six months

Remission : The state of remission constitutes a clinical condition in which no active disease is present

1. CDAI (clinical Disease Activity Index) ≤ 2.8 (calculated by specific calculater) OR
2. All of the following:
   - Swollen and tender joint counts (using 28 joint count) each ≤1
   - Patient global assessment (on a 0 to 10 scale) ≤1

Treatment of Early, Mildly Active Rheumatoid Arthritis

Patients with mild disease meet the ACR criteria for RA and typically have all of the following:

- Fewer than six inflamed joints
- No extraarticular disease
- No evidence of erosions or cartilage loss on plain radiographs.

- **NSAID** at full therapeutic dose, unless contraindicated by gastrointestinal or renal disease or heart failure. Dose of NSAIDs is titrated to optimum tolerated level and continued for at least two weeks.

  Diclofenac potassium: 50 mg PO q8-12hr

  Diclofenac sodium: 50 mg PO q8hr or 75 mg PO q12hr

  Ibuprofen 300 mg, 400 mg, 600 mg, or 800 mg PO q6-8hr; not to exceed 3200 mg/day

NSAIDs do not prevent development of erosive disease in patients with continued disease activity. Thus, in the presence of signs of persistent synovitis, it is recommended that one or more DMARD be added to the pharmacologic regimen within 6 weeks to 3 months of continued symptoms and/or signs of disease.

- **Systemic glucocorticoids** such as oral prednisone or prednisolone are used sparingly in patients with early, mildly active RA.
  Oral doses equivalent to 7.5 mg/day or less of prednisolone are relatively safe for short duration (several months or less). Higher doses are more effective in relieving joint pain and tenderness and have a greater effect on these manifestations than do NSAIDs but also have a greater risk of side effects .

  Doses >7.5 mg/day should be used for the shortest time possible
  Early use of glucocorticoids followed by rapid reduction in dose and then discontinuation, in combination with sustained use of a regimen of nonbiologic DMARDs that includes MXT is superior to monotherapy with nonbiologic DMARDs.

- We initiate DMARD therapy early in treatment of RA because delayed use of such medications results in poorer physical function and increased joint injury .
  Try to use a DMARD that has a relatively low risk of serious adverse effects.

  Antimalarial drugs may be appropriate in selected patients with early, mildly active RA, particularly those lacking poor prognostic features . Such patients have fewer joints involved, and less swelling and tenderness.
  Hydroxychloroquine 200 to 400 mg/day, with a maximum dose of 6.5 mg/kg/day
  Administration of hydroxychloroquine commonly results in clinical improvement by 2 to 3 months, but maximum effects may require up to 4 -6 months of therapy.

  More potent DMARDs such as **MXT** and **leflunomide**, and biologic DMARDs, such as TNF inhibitors, are not used in patients with early, mildly active disease unless disease activity persists.

  Reevaluation — Patients with early, mildly active RA should be reevaluated every 3 -5 weeks for effectiveness of therapy and to monitor for possible drug toxicity. These visits also provide an opportunity for patient education and other interventions noted above.

  Patients with relatively less or more severe disease may be afforded more or less time for a therapeutic response, respectively, prior to entertaining more aggressive therapy.

Treatment of Early, Moderately Active RA

Patients with moderately active RA, by definition, do not fulfill criteria for either mildly or severely active disease. They are at greater risk of developing joint damage and disability than patients with mildly active disease. Patients with moderately active disease typically have between 6 and 20 inflamed joints plus some combination of the following clinical features:

- Absence of extraarticular disease (most common)
- Elevation in ESR and/or serum CRP concentration
- Positive rheumatoid factor and/or anti- CCP antibodies
- Evidence of inflammation on plain radiography, such as osteopenia and/or periarticular swelling; in addition, minimal joint space narrowing and small peripheral erosions may be observed.

- **Use of nonsteroidal antiinflammatory drugs**
  Dose of NSAIDs is titrated to the optimum tolerated level and the patient is then followed for at least two weeks. Patients whose disease is poorly controlled or flares on one agent, may respond to another NSAID. Patients should be cautioned regarding the risks of chronic use of NSAIDs.

- **Nonbiologic DMARDs**: hydroxychloroquine, methotrexate, and leflunomide alone or in combination.

  Decision to add a DMARD depends upon relative activity of disease, such as number of inflamed joints, severity of inflammation, number of poor prognostic signs, and the degree of functional impairment.

- Patients who lack poor prognostic features and are at the milder end of spectrum of disease activity (fewer joints involved and less swelling and tenderness) → **Hydroxychloroquine** may be appropriate 200 to 400 mg/day, maximum dose of 6.5 mg/kg/day.

- In patients with high disease activity and features associated with a poor prognosis.

  Methotrexate is commonly selected as early therapy EXCEPT for patients with liver disease and women who are willing to become pregnant or are pregnant. MTX typically serves as the "anchor" drug for most commonly used DMARD combinations.It has a faster onset of action, comparable or greater efficacy, and better long-term tolerance than other nonbiologic DMARD monotherapy.

  Dose: 7.5 - 15 mg once weekly depending on degree of disease activity, size and age of patient, presence of comorbidities, and renal function. Usual approach to dose titration is to increase dose after 4 weeks at a rate of 2.5 mg /week as indicated by disease activity and as tolerated. Maximum dose is 25 mg/week.

  A lower initial dose is warranted in patients with reduced renal function (eGFR <60 mL/min) .

  For patients in whom 25 mg once weekly is ineffective or poorly tolerated because of GI symptoms, a trial of **SQ MXT** is an alternative to switching to another DMARD or addition of TNF inhibitor.

  Alternatively, MTX is better absorbed, particularly at doses higher than 20 mg/week, if dose is split into two doses on the day of administration. It is imperative to tell the patient to take all MTX over a single 24-hour period once a week, as spreading the dose out further may produce significant liver toxicity.

- **In patients with active disease despite MXT** , addition of leflunomide, hydroxychloroquine has been shown to be superior to MXT alone.

- For those with contraindications to use of MTX, Leflunomide can be effective alternative
  Dose: PO 100 mg once daily for 3 days, followed by 20 mg once daily (max 20 mg/day). If dosing at 20 mg/day is not well tolerated, the dosage may be decreased to 10 mg/day; carefully observe the patient because it may take several weeks for metabolite levels to decline.

- **Use of adjunctive therapies** to NSAIDs and DMARDs, such oral **glucocorticoids**
  Up to 7.5 mg/day of **prednisone** should be considered in management of acute flares as it's shown to retards radiologic progression in patients with RA in short to medium term . Once patient has improved, glucocorticoid dose should be slowly tapered over a period of a few months, as tolerated, and then completely discontinued if possible.

- **Other DMARDs that can be added to MXT combination therpy**

  Cyclosporine 1.25 mg/kg PO BID; may increase by 0.5-0.75 mg/kg/day after 8 weeks and again after 12 weeks if needed, not to exceed 4 mg/kg/day. Discontinue if no improvement observed by 16 weeks.

  Azathioprine :1 mg/kg/day IV/PO initially in single daily dose or divided q12hr; may be increased by 0.5 mg/kg/day after 6-8 weeks, then by 0.5 mg/kg/day every 4 weeks; not to exceed 2.5 mg/kg/day
  Maintenance: Reduce daily dose by 0.5 mg/kg every 4 weeks until lowest effective dosage is reached

- **If no adequate response to nonbiologic DMARDs**, particularly those with a poor prognosis, TNF-α inhibitors may be considered as an alternative to DMARD combinations.

Etanercept alone : 50 mg SC once weekly or 25 mg SC twice weekly; if twice weekly, doses should be given on same day or 3-4 days apart
Or Adalimumab alone if etanercept failed: 40 mg SC every 2 weeks ,

Reevaluation : disease activity and the response to therapy should be regularly reassessed every three to five weeks. More aggressive therapy should be if the disease remains active or progresses.

Treatment of Early, Severely Active RA

Compared with those with relatively milder disease, patients with severely active RA have a larger number of inflamed joints, are more likely to be RF- and anti- CCP antibody-positive, and to have early bony erosions, and may have extraarticular and/or systemic manifestations:

- Patients have more than 20 inflamed joints on complete joint examination, the hallmarks of which are warmth, swelling, and evidence of a joint effusion. Only warmth and tenderness of the joint may be evident on examination in rare patients, and erythema is usually absent.

- Patients also typically exhibit an elevation in ESR and/or serum CRP, and ≥ 1 of the following:

1. Anemia of chronic disease and/or hypoalbuminemia
2. Rheumatoid factor positivity (often in high titer) and/or anti- CCP antibodies
3. Joint radiographs demonstrating rapid appearance of bony erosions and loss of cartilage
4. Extraarticular disease

- Initiate therapy with a **DMARD** or combinations of DMARDs: MTX as initial DMARD .

  MTX is recommended as the DMARD of first choice in early, severely active RA.
  Initiate therapy at a dose between 7.5 and 15 mg once weekly for most patients
  We increase dose each week after 4 weeks at a rate of 2.5 mg (one tablet)/week, as tolerated and as indicated by disease activity. The maximum dose is 25 mg/week. An alternative initial schedule used by some rheumatologists for severely active disease is an increase each week in the oral MTX dose after the first four weeks by 5 mg weekly to a maximum dose of 25 mg/week.

- Add **NSAIDs** or systemic glucocorticoids when needed for initial control of inflammation, while awaiting the response to DMARDs, but should not be used as the sole or primary treatment. There is no evidence that NSAIDs limit disease progression. **Glucocorticoids** should not be used alone for an extended since they are associated with increased morbidity and mortality.
  - ✓ **Prednisone**, 10 to 15 mg/day, and increase dose as required to up to 30 mg/day if the patient does not respond adequately to the initial lower dose. It should be tapered as rapidly as tolerated, with the goal of their discontinuation once disease control is achieved and can be maintained.
    A goal of successful DMARD therapy is the reduction or discontinuation of glucocorticoids.
  - ✓ Some patients must avoid daily oral glucocorticoids or require an extremely rapid antiinflammatory response →a single initial **IM** injection of **methylprednisolone** 80 - 120 mg
    Up to 2 subsequent injections q 4 weeks can maintain improvement in symptoms, signs, and physical function, while slower acting DMARDs exert their expected effect on controlling disease activity.

- If response to appropriate doses of MTX monotherapy is inadequate after **3** months or if there are persistently high levels of disease activity on MTX alone, preferred approach is to initiate combination consisting of **MTX + HCQ**; or **MTX + Leflunamide** or **LEF** in place of MTX.

- In patient who is unable to take MTX or DMARDs combination therapy is ineffective, add **TNF-α** inhibitor alone or to MXT. There is no evidence that any one of TNF inhibitors has greater efficacy than the others. Choice depends upon safety issues and patient preference for route and/or frequency of injection:

  – **Etanercept** is prefered first because of its similar efficacy compared with MTX, and longer experience or evidence of lower rates of serious infections compared with other biologics
  – **Adalimumab** is also effective if patient preference for an every other week injection over a weekly injection overrides the other considerations noted above that would favor etanercept
  – **An inadequate response to one anti-TNF agent** does not predict resistance to other agents in this class, although loss of efficacy and discontinuation rates increase with successive switches. Thus, we suggest discontinuing the first TNF inhibitor if disease activity is not adequately controlled after a three-month trial and using a second TNF inhibitor.

- In those who do not respond to this regimen, we administer **rituximab** alone or with MXT

  1000 mg IV infusion, repeat after 2 week (2 infusions separated by 2 week is 1 course)
  Repeat course q24weeks or based on clinical evaluation (but no sooner than 16 weeks)

- Most patients require sustained therapy over months to years to achieve treatment goals. We prefer to continue nonbiologic and biologic DMARD therapy at reduced doses, if possible, but do not discontinue DMARD therapy in most patients who have had severely active RA.

  Evaluation of response to therapy: patients should therefore be seen and assessed at least every two to three months in addition to appropriate laboratory monitoring for medication toxicities.

Treatment of Persistently Active RA

Persistently active RA refers to disease of ≥6 months' duration that has continued despite the use of methotrexate or other DMARDs.

The patient with persistently active RA despite appropriate treatment remains a significant challenge, regardless of disease severity. Such patients will have often received anti-inflammatory doses of NSAIDs, low-dose glucocorticoids, and one or more DMARDs. Therapeutic options in this setting are often complex and potentially more risky, and referral to a rheumatologist is recommended.

Most patients with persistently active RA will receive a **combination** of nonbiologic DMARDs or a combination of nonbiologic and biologic DMARDs. Combinations of biologics should be avoided, since they produce disproportionately greater increases in risk than benefit.

One of the following approaches is suggested if MXT therapy is inadequate :

- MTX and HCQ combination therapy
- LEF plus MTX or LEF in place of MTX.
- If a satisfactory response is not observed within *3 months*, a **TNF inhibitor** is given, HCQ or LEF are withdrawn, and glucocorticoids are tapered as tolerated, leaving a combination regimen of MTX and a TNF inhibitor.
- If disease activity is not adequately controlled after *a 3-month* trial and using a **second TNF** inhibitor. In such patients, we usually use either adalimumab or etanercept
- In patients who don't respond to the second TNF inhibitor, it is primarily for the same reason that first drug was stopped (inefficacy or toxicity) .Because likelihood of a response decreases with second switches of TNF inhibitors, a change in biologic DMARD drug class is suggested after the failure of two such agents → option is **rituximab**, which depletes B cells

Resistance to all above therapies — In patients who fail all of the above regimens, hematopoietic stem cell transplantation is being evaluated in clinical trials.

Drug Therapy For Flares

Naturally occurring disease exacerbations (flares) often occur on a background of active disease and it is important to distinguish a disease flare, characterized by symptoms and physical and laboratory findings of increased inflammatory synovitis, from noninflammatory causes of local or generalized increased pain.

- In patients with a single or few affected joints, **intraarticular glucocorticoid** injections may be effective and avoid the need for additional or prolonged systemic therapy.
- More widespread flares may be treated with an increase in the dose of **oral glucocorticoid**, with the intention of reducing the dose once the flare is under control. The magnitude of dose increase varies with the baseline dose and the severity of the flare. An alternative to increasing the oral dose is a single intramuscular injection of depot **methylprednisolone** acetate.
- Pulse IV **methylprednisolone**, usually consisting of 3 daily infusions of up to 1000 mg is generally limited to severe flares such as rheumatoid vasculitis.
- Patients on **MTX** who will tolerate a slower resolution of their flare may respond to an increase in the dose of MTX or a switch from oral to SQ therapy .
- Increases in doses of etanercept (> 50 mg weekly), or adalimumab (weekly rather than every two weeks), with or without MTX, do not appear to have greater efficacy.

Therapy Of End Stage Disease

Despite therapeutic interventions described above, some patients progress to disabling, destructive joint disease.Exacerbations and systemic toxicity are usually easily recognized by the presence of many inflamed joints, fever, anemia, or an elevated ESR or serum CRP concentration.

The goals of therapy in the patient with end-stage disease are: pain relief, protection of remaining articular structures , maintenance of function, relief from fatigue and weakness.

The indications for surgical intervention in patients with RA : intractable pain or severe functional disability due to joint destruction, and impending tendon rupture.

Rheumatoid Arthritis And Pregnancy

Pregnancy related changes in circulating hormones may contribute to alterations in immune system that may impact disease activity. Approximately 50 to 80 % of women with RA improve during pregnancy. The decrease in disease activity generally starts in first trimester and lasts for a number of weeks or months into postpartum period.

Postpartum flare: ~ 90 % of patients flare during postpartum period, usually within the first 3 months. Many clinicians advocate reintroducing medications in the immediate postpartum period because the stress of caring for a newborn can be compounded by the possibility of an RA flare.

Breastfeeding: Some clinicians believe that breastfeeding increases risk of RA and that the risk is higher following first pregnancies.

Pregnancy outcome: women with RA (or other inflammatory arthritis) who experience a higher level of disease activity during the third trimester and/or take glucocorticoids are at risk for small gestational age babies and preterm delivery .

Medications typically used for RA may be divided into 3 categories:

1. **Drugs with a moderate to high risk of fetal harm**: Methotrexate ,Leflunomide : should be stopped 1 to 3 months prior to conception.
2. **Drugs that may be used selectively during pregnancy**
   - **Glucocorticoids** to manage flares or persistent moderate to highly active disease: prednisolone and methylprednisolone → relatively safe in low to moderate doses (not > 10 mg/day).
     Patients should be counseled that use of glucocorticoids before 14 weeks of gestation can increase the risk of cleft palate formation and can contribute to pregnancy-induced HTN and gestational diabetes later during pregnancy.

   - **NSAIDs** and **aspirin** can be used safely during pregnancy at certain times, but not others. Use of NSAIDs or aspirin near the time of conception or during early pregnancy may interfere with implantation. Thus, these agents should be avoided during a conception cycle and early pregnancy.NSAIDs may be used in the first trimester after a positive pregnancy test and during the second trimester, but should be avoided during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and inhibition of labor.

   - **TNF inhibitors and rituximab** may be used if disease is not adequately controlled by other measures and benefit outweighs risk **.**

3. **Drugs with minimal fetal and maternal risk**: Hydroxychloroquine can be used in patients with inadequate response to NSAIDs or prednisone.

Medication use during breastfeeding

- ✓ NSAIDs can be used, but aspirin should be avoided.
- ✓ Prednisone can be taken in low doses. In patients taking 20 mg/day or more, it is recommended to wait four hours after the dose prior to nursing.
- ✓ Azathioprine, cyclosporine, methotrexate should be avoided in nursing women

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis (JRA) is the most common chronic rheumatologic disease in children and is one of the most common chronic diseases of childhood. The etiology is unknown, and the genetic component is complex, making clear distinctions between the various subtypes difficult.

Although JIA is defined as arthritis beginning before age 16 years, the age at onset is often much lower, with the highest frequency occurring in children aged 1-3 years. This age distribution is most evident in girls with oligoarticular JIA and psoriatic arthritis.

Physical findings:

- Arthritis: Defined either as intra-articular swelling on examination or as limitation of joint motion in association with pain, warmth, or erythema of the joint; physical findings in JIA reflect the extent of joint involvement
- Synovitis: Characterized by synovial proliferation and increased joint volume; the joint is held in a position of maximum comfort, and range of motion often is limited only at the extremes

Types of JIA include the following:

- Systemic-onset juvenile idiopathic arthritis
- Oligoarticular juvenile idiopathic arthritis
- Polyarticular juvenile idiopathic arthritis
- Psoriatic arthritis
- Enthesitis-related arthritis
- Undifferentiated arthritis

Management

- ✓ Pharmacologic therapy with NSAIDs, DMARDs, biologic agents, or oral corticosteroids
- ✓ Psychosocial interventions
- ✓ Measures to enhance school performance (eg, academic counseling)
- ✓ Improved nutrition
- ✓ Physical therapy
- ✓ Occupational therapy

ACR recommends treatment approaches to JIA on basis of the following 5 treatment groups:

1. A history of arthritis in 4 or fewer joints
2. A history of arthritis in 5 or more joints
3. Active sacroiliac arthritis
4. Systemic arthritis without active arthritis
5. Systemic arthritis with active arthritis

A history of arthritis in 4 or fewer joints

In this treatment group, escalation of therapy typically proceeds from NSAIDs to intra-articular glucocorticoid injections to methotrexate to TNF-α inhibitors.

NSAIDs alone may be adequate for patients with involvement of a single joint and other indications of low disease activity (eg, normal inflammatory marker levels); response should be evident within 2 months. For other patients, NSAIDs may be used as adjunctive treatment, as needed.

–Diclofenac : > 3 years: 2-3 mg/kg qDay for up to 4 weeks

–Ibuprofen :30-50 mg/kg/24hr PO divided q8hr; not to exceed 2.4 g/day

Intra-articular injections of triamcinolone can be used for any joint involved with active arthritis, and should provide clinical relief for at least 4 months. If so, injections can be repeated as needed.

Methotrexate can be instituted in patients who fail to show adequate response to NSAIDs and/or joint injections. Alternatively, MXT is recommended as initial treatment for patients in this treatment group who have high disease activity and features indicating poor prognosis.

Initial: 10 mg/m² PO/IM/SC qWeek

>20 mg/m²/wk might affect risk of serious toxicity in children

Other DMARDs can be used with MXT :

Azathioprine : 1 mg/kg/day IV/PO initially in single daily dose or divided q12hr; may be increased by 0.5 mg/kg/day after 6-8 weeks, then by 0.5 mg/kg/day every 4 weeks; not to exceed 2.5 mg/kg/day

Maintenance: Reduce daily dose by 0.5 mg/kg every 4 weeks until lowest effective dosage is reached

Patients in this treatment group who fail to respond adequately to joint injections and to 3-6 months (depending on disease characteristics and severity) of MXT are candidates for TNF-α treatment.

Etanercept : 2-17 years: 0.8 mg/kg SC weekly; not to exceed 50 mg weekly

Or Adalimumab : may be administered with MXT, glucocorticoids, NSAIDs, or analgesics

≥4 years: ≥15 kg, <30 kg: 20 mg SC every 2 weeks
≥30 kg: 40 mg SC every 2 weeks

Safety and effectiveness of rituximab in JRA not established; FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients <16 years due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system.

History of Arthritis in 5 or More Joints

Treatment in this group places less emphasis on initial **NSAIDs**. After 1 month of NSAID treatment in patients with low disease activity, or 1-2 months in those with moderate disease activity but without poor prognostic features (ie, hip or cervical spine involvement, positive RF or anti-CCP antibodies, radiographic signs of joint damage), it is appropriate to escalate to MXT, plus adjunctive NSAIDs and joint injection as needed.

In patients with moderate disease activity and poor prognostic features, as well as in patients with high disease activity, treatment may start with **methotrexate**.

Leflunomide may be used as an alternative to methotrexate, after a failed NSAID trial, or as initial treatment in patients with high disease activity and poor prognostic features.

Escalation to a **TNF-α inhibitor** follows if 3-6 months (depending on disease characteristics and severity) of methotrexate or leflunomide provides inadequate control.

Patients who show inadequate response after 3-4 months (depending on disease characteristics and severity) of TNF-α inhibitor treatment can be switched to a different TNF-α inhibitor .

Active Sacroiliac Arthritis

Use of a TNF-α inhibitor is recommended more readily for patients in this group. A TNF-α inhibitor may be started after failure of an adequate trial of **NSAIDs** or after 3-6 months (depending on disease characteristics and severity) of **methotrexate** proves inadequate.

Systemic Arthritis with Active Systemic Features and without Active Arthritis

A 2-week trials of **NSAIDs** may be used in patients who have fever and less severe disease, and have had significant active systemic disease for less than 6 months; after that, patients should be started on systemic **glucocorticoids**, with adjunct NSAIDs as needed.Patients with high systemic disease activity (eg, significant serositis) may be started on steroids as a first step.

Systemic Arthritis with Active Arthritis and without Active Systemic Features

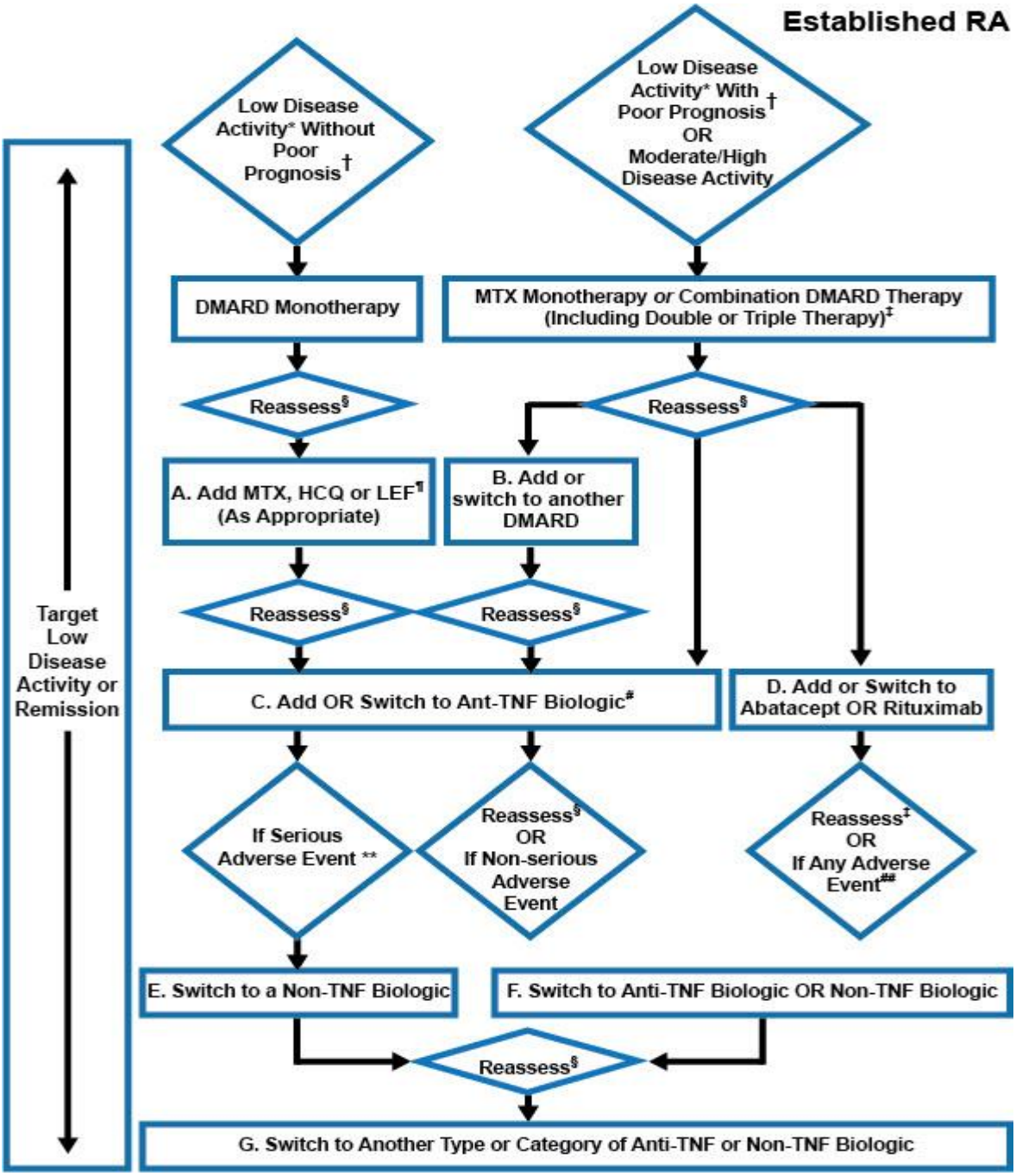
NSAID therapy, with intra-articular joint injections as needed, may be adequate for patients with low disease activity who do not have hip involvement or radiographic signs of joint damage. After up to 1 month, however, **methotrexate** can be added for patients with any degree of disease severity who continue to have active arthritis.

After 3 months of methotrexate therapy, the next step in escalation is TNF-α inhibitor, although **etanercept** is less effective in systemic arthritis than in other forms of JIA.

Procedures that may be considered in specific circumstances when previous measures fails include:

- Synovectomy
- Osteotomy and arthrodesis
- Hip and knee replacement

Rheumatoid Arthritis Algorithm



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