

Rheumatoid Arthritis

Diagnosis and Current Management

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Introduction

- Commonest inflammatory joint disease seen in clinical practice affecting approx 1% of population.
- Chronic multisystem disease of unknown cause.
- Characterized by persistent inflammatory synovitis leading to cartilage damage, bone erosions, joint deformity and disability.

Onset

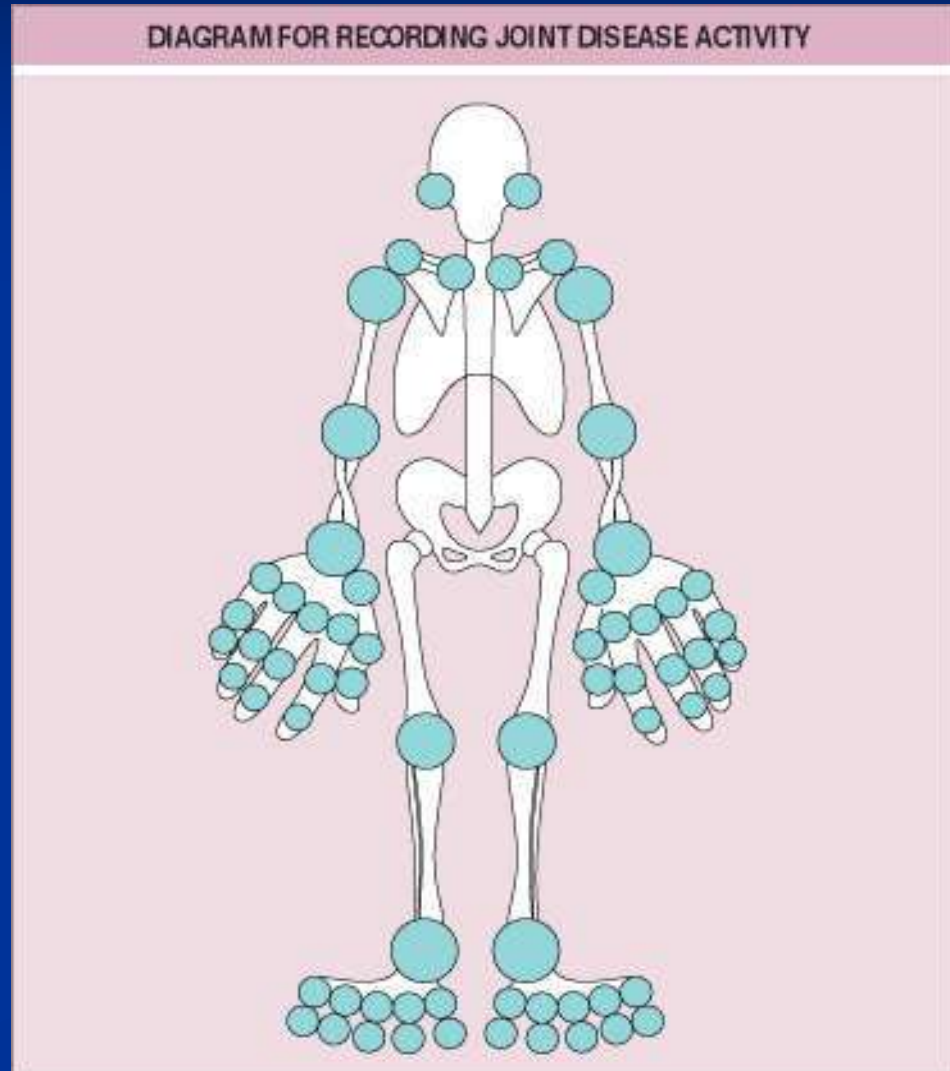
- Although Rheumatoid arthritis may present at any age, patients most commonly are first affected in the **third to sixth** decades.
- **Female: male 3:1**
- Initial pattern of joint involvement could be:-
 - 1) Polyarticular : most common
 - 2) Oligoarticular
 - 3) Monoarticular
- **Morning joint stiffness > 1 hour** and easing with physical activity is characteristic.
- **Small joints of hand and feet** are typically involved.

Clinical Manifestations

- Articular
- Extra-articular

Articular manifestation

- Pain in affected joint aggravated by movement is the most common symptom.
- Morning stiffness ≥ 1 hr
- Joints involved ->



Relative incidence of joint involvement in RA

- MCP and PIP joints of hands & MTP of feet 90%
- Knees, ankles & wrists- 80%
- Shoulders- 60%
- Elbows- 50%
- TM, Acromio - clavicular & SC joints- 30%

Joints involved in RA

- Don't forget the **cervical spine**!!
Instability at cervical spine can lead to impingement of the spinal cord.
- Thoracolumbar, sacroiliac, and distal interphalangeal joints (DIP) of the hand are **NOT** involved.

PIP Swelling

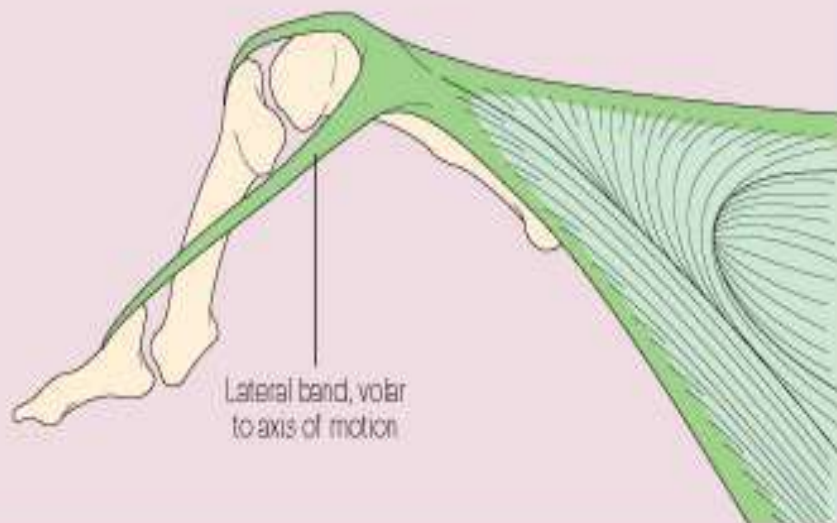


Ulnar Deviation, MCP Swelling, Left Wrist Swelling

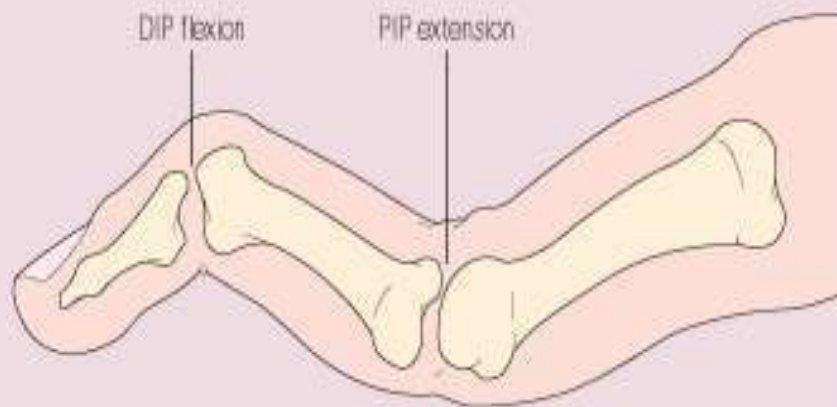


BOUTONNIERE AND SWAN-NECK DEFORMITIES

Boutonniere deformity



Swan-neck deformity





Extra-articular manifestations

- Present in 30-40%
- May occur prior to arthritis
- Patients that are more likely to get are:
 - High titres of RF/ anti-CCP
 - HLA DR4+
 - Male
 - Early onset disability
 - History of smoking

Extraarticular Involvement

- **Constitutional symptoms** (most common)
- **Rheumatoid nodules**(30%)
- **Hematological-**
 - normocytic normochromic anemia
 - leucocytosis /leucopenia
 - thrombocytosis
- ***Felty's syndrome-***
 - Chronic nodular Rheumatoid Arthritis
 - Splenomegaly
 - Neutropenia

- **Respiratory**- pleural effusion, pneumonitis , pleuro-pulmonary nodules, ILD
- **CVS**-asymptomatic pericarditis , pericardial effusion, cardiomyopathy
- **Rheumatoid vasculitis**- mononeuritis multiplex, cutaneous ulceration, digital gangrene, visceral infarction
- **CNS**- peripheral neuropathy, cord-compression from atlantoaxial/midcervical spine subluxation, entrapment neuropathies
- **EYE**- kerato conjunctivitis sicca, episcleritis, scleritis



Rheumatoid nodule

Laboratory investigations in RA

- CBC- TLC, DLC, Hb, ESR & GBP
- Acute phase reactants
- Rheumatoid Factor (RF)
- Anti- CCP antibodies

Rheumatoid Factor (RF)

- Antibodies that recognize Fc portion of IgG
- Can be IgM , IgG , IgA
- 85% of patients with RA over the first 2 years become RF+
- A negative RF may be repeated 4-6 monthly for the first two year of disease, since some patients may take 18-24 months to become seropositive.
- **PROGNOSTIC VALUE-** Patients with high titres of RF, in general, tend to have **POOR PROGNOSIS, MORE EXTRA ARTICULAR MANIFESTATION.**

Causes of positive test for RF

- Rheumatoid arthritis
- Sjogrens syndrome
- Vasculitis such as polyarteritis nodosa
- Sarcoidosis
- Systemic lupus erythematosus
- Cryoglobulinemia
- Chronic liver disease
- Infections- tuberculosis , bacterial endocarditis, infectious mononucleosis, leprosy, syphilis, leishmaniasis.
- Malignancies
- Old age(5% women aged above 60)

Anti-CCP

- IgG against synovial membrane peptides damaged via inflammation
- Sensitivity (65%) & Specificity (95%)
- **Both diagnostic & prognostic value**
- Predictive of Erosive Disease
 - Disease severity
 - Radiologic progression
 - Poor functional outcomes

Acute Phase Reactants

Positive acute phase reactants (↑)	Negative acute phase reactants (↓)
<p data-bbox="112 362 459 415">Mild elevations</p> <ul data-bbox="189 454 736 608" style="list-style-type: none"><li data-bbox="189 454 600 511">– Ceruloplasmin<li data-bbox="189 544 736 608">– Complement C₃ & C₄ <p data-bbox="112 634 581 686">Moderate elevations</p> <ul data-bbox="189 725 823 1058" style="list-style-type: none"><li data-bbox="189 725 587 782">– Haptoglobin<li data-bbox="189 815 658 872">– Fibrinogen (ESR)<li data-bbox="189 905 774 962">– α₁ – acid glycoprotein<li data-bbox="189 995 823 1052">– α₁ – proteinase inhibitor <p data-bbox="112 1086 533 1139">Marked elevations</p> <ul data-bbox="189 1178 846 1322" style="list-style-type: none"><li data-bbox="189 1178 823 1235">– C-reactive protein (CRP)<li data-bbox="189 1268 846 1325">– Serum amyloid A protein	<ul data-bbox="981 362 1302 505" style="list-style-type: none"><li data-bbox="981 362 1244 419">– Albumin<li data-bbox="981 452 1302 505">– Transferrin

Other Lab Abnormalities

- Elevated APRs(ESR, CRP)
- Thrombocytosis
- Leukocytosis
- ANA
 - 30-40%
- Inflammatory synovial fluid
- Hypoalbuminemia

Radiographic Features

- Peri-articular osteopenia
- Uniform symmetric joint space narrowing
- Marginal subchondral erosions
- Joint Subluxations
- Joint destruction
- Collapse

- **Ultrasound** detects early soft tissue lesions.
- **MRI** has greatest sensitivity to detect synovitis and marrow changes.







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Diagnostic Criterias

ACR Criteria (1987)

- 1. Morning Stiffness ≥ 1 hour
- 2. Arthritis of ≥ 3 joints observed by physician simultaneously-
Rt/Lt-PIP, MCP, wrist, elbow, knee, ankle, MTP
- 3. Arthritis of hand joints-PIP, MCP, wrist
- 4. Symmetric arthritis
- 5. Rheumatoid nodules
- 6. Positive Rheumatoid Factor
- 7. Radiographic Erosions or periarticular osteopenia in hand or wrist joints
- Criteria 1-4 must be present for ≥ 6 wks
- Must have ≥ 4 criteria to meet diagnosis of RA

2010 ACR/EULAR Classification Criteria

- a score of $\geq 6/10$ is needed for classification of a patient as having definite RA
- **A. Joint involvement** **SCORE**
- 1 large joint 0
- 2–10 large joints 1
- 1–3 small joints (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)^{††} 5

- **B. Serology** (at least 1 test result is needed for classification)
- Negative RF *and* negative ACPA 0
- Low-positive RF *or* low-positive ACPA 2
- High-positive RF *or* high-positive ACP 3

- **C. Acute-phase reactants** (at least 1 test result is needed for classification)
- Normal CRP *and* normal ESR 0
- Abnormal CRP *or* normal ESR 1

- **D. Duration of symptoms**
- <6 weeks 0
- ≥ 6 weeks 1

Management

Goals of management

- Focused on relieving pain
- Preventing damage/disability
- Patient education about the disease
- Physical Therapy for stretching and range of motion exercises
- Occupational Therapy for splints and adaptive devices
- Treatment should be started early and should be individualised .
- ***EARLY AGGRESSIVE TREATMENT***

Treatment modalities for RA

- NSAIDS
- Steroids
- DMARDs
- Immunosuppressive therapy
- Biological therapies
- Surgery

NSAIDS

Non-Steroidal anti-inflammatories (NSAIDS) / Coxibs for symptom control

- 1) Reduce pain and swelling by inhibiting COX
- 2) Do not alter course of the disease.
- 3) Chronic use should be minimised.
- 4) Most common side effect related to GI tract.

Corticosteroids in RA

- Corticosteroids , both systemic and intra-articular are important adjuncts in management of RA.
- Indications for systemic steroids are:-
 1. For treatment of rheumatoid flares.
 2. For extra-articular RA like rheumatoid vasculitis and interstitial lung disease.
 3. As *bridge therapy* for 6-8 weeks before the action of DMARDs begin.
 4. Maintenance dose of 10mg or less of prednisolone daily in patients with active RA.
 5. Sometimes in pregnancy when other DMARDs cannot be used.

Disease Modifying Anti-rheumatic Agents

- Drugs that actually alter the disease course .
- Should be used as soon as diagnosis is made.
- Appearance of benefit delayed for weeks to months.
- NSAIDS must be continued with them until true remission is achieved .
- Induction of true remission is unusual .

DMARDs

Commonly used	Less commonly used
Methotrexate	Chloroquine
Hydroxychloroquine	Gold(parenteral & oral)
Sulphasalazine	CyclosporineA
Leflunomide	D-penicillamine/bucillamine
	Minocycline/Doxycycline Levamisole
	Azathioprine, cyclophosphamide, chlorambucil

Clinical information about DMARDs

NAME	DOSE	SIDE EFFECTS	MONITORING	ONSET OF ACTION
1) Hydroxychloroquine	200mg twice daily x 3 months, then once daily	Skin pigmentation, retinopathy, nausea, psychosis, myopathy	Fundoscopy & perimetry yearly	2-4 months
2) Methotrexate	7.5-25 mg once a week orally, s/c or i/m	GI upset, hepatotoxicity, Bone marrow suppression, pulmonary fibrosis	Blood counts, LFT 6-8 weekly, Chest x-ray annually, urea/creatinine 3 monthly; Liver biopsy	1-2 months

Clinical information about DMARDs contnd..

NAME	DOSE	SIDE EFFECTS	MONITORING	ONSET OF ACTION
3) Sulphasalazine	2gm daily p.o	Rash, myelosuppression, may reduce sperm count	Blood counts ,LFT 6-8 weekly	1-2 months
4) Leflunomide	Loading 100 mg daily x 3 days, then 10-20 mg daily p.o	Nausea, diarrhoea, alopecia, hepatotoxicity	LFT 6-8 weekly	1-2 months

When to start DMARDs?

- DMARDs are indicated in all patients with RA who continue to have active disease even after 3 months of NSAIDS use.
- The period of 3 months is arbitrary & has been chosen since a small percentage of patients may go in spontaneous remission.
- The vast majority , however , need DMARDs and many rheumatologists start DMARDs from *Day 1*.

How to select DMARDs?

- There are no strict guidelines about which DMARDs to start first in an individual.
- Methotrexate has rapid onset of action than other DMARD.
- Taking in account patient tolerance, cost considerations and ease of once weekly oral administration **METHOTREXATE is the DMARD of choice**, most widely prescribed in the world.

Should DMARDs be used singly or in combination?

- Since single DMARD therapy (in conjunction with NSAIDS) is often only modestly effective , combination therapy has an inherent appeal.
- DMARD combination is specially effective if they include *methotrexate* as an anchor drug.
- **Combination of methotrexate with leflunamide** are synergistic since their mode of action is different.

Limitations of conventional DMARDs

- 1) The onset of action takes several months.
 - 2) The remission induced in many cases is partial.
 - 3) There may be substantial toxicity which requires careful monitoring.
 - 4) DMARDs have a tendency to lose effectiveness with time-(slip out).
- These drawbacks have made researchers look for alternative treatment strategies for RA- **The Biologic Response Modifiers.**

Immunosuppressive therapy

Agent	Usual dose/route	Side effects
<i>Azathioprine</i>	50-150 mg orally	GI side effects , myelosuppression, infection,
<i>Cyclosporin A</i>	3-5 mg/kg/day	Nephrotoxic , hypertension , hyperkalemia
<i>Cyclophosphamide</i>	50 -150 mg orally	Myelosuppression , gonadal toxicity ,hemorrhagic cystitis , bladder cancer

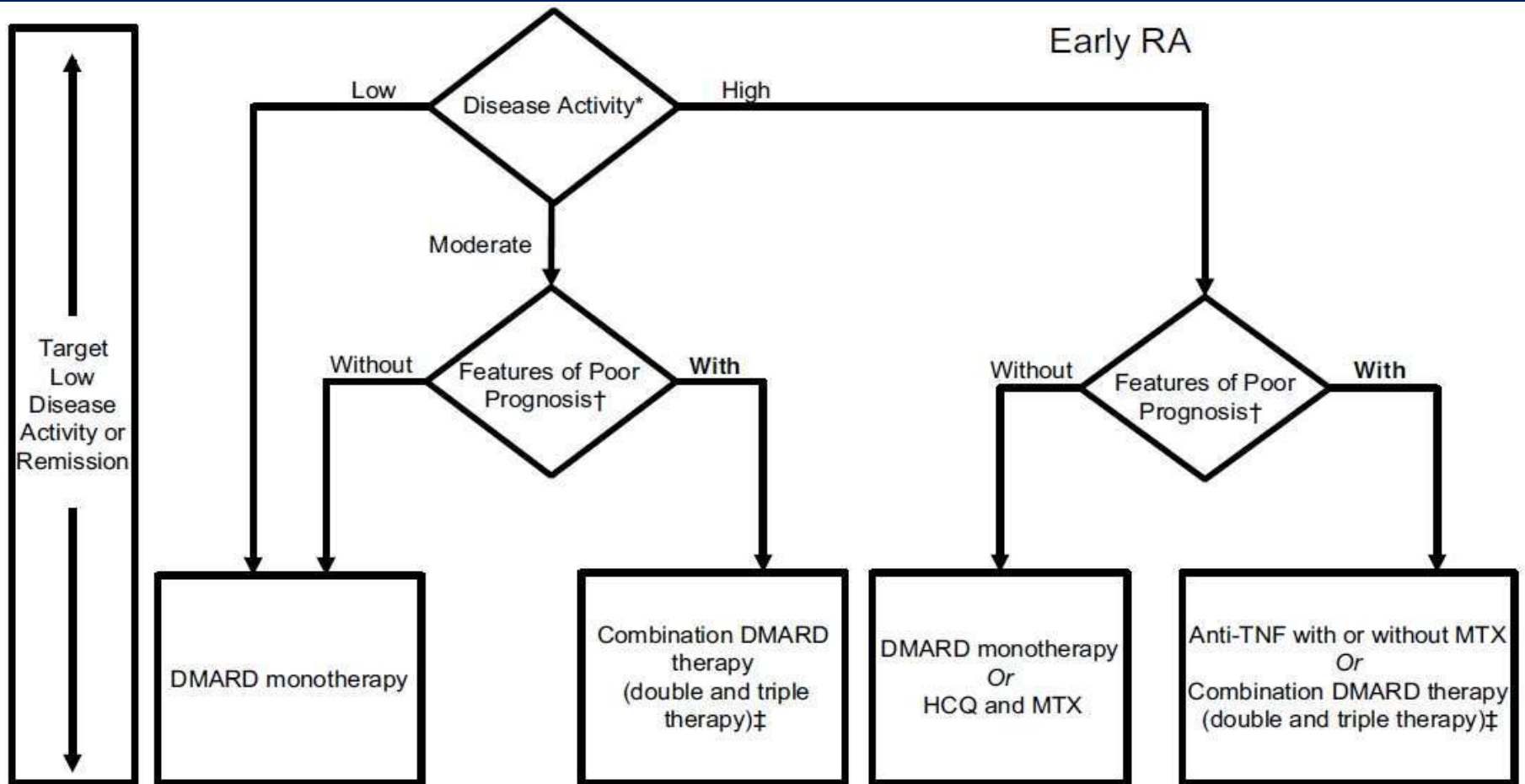
BIOLOGICS IN RA

- Cytokines such as TNF- α ,IL-1,IL-10 etc. are key mediators of immune function in RA and have been major targets of therapeutic manipulations in RA.
- Of the various cytokines,TNF- α has attracted maximum attention.
- Various biologicals approved in RA are:-
 - 1) **Anti TNF agents** : Infliximab Etanercept Adalimumab
 - 2) **IL-1 receptor antagonist** : Anakinra
 - 3) **IL-6 receptor antagonist** : Tocilizumab
 - 4) **Anti CD20 antibody** : Rituximab
 - 5) **T cell costimulatory inhibitor** : Abatacept

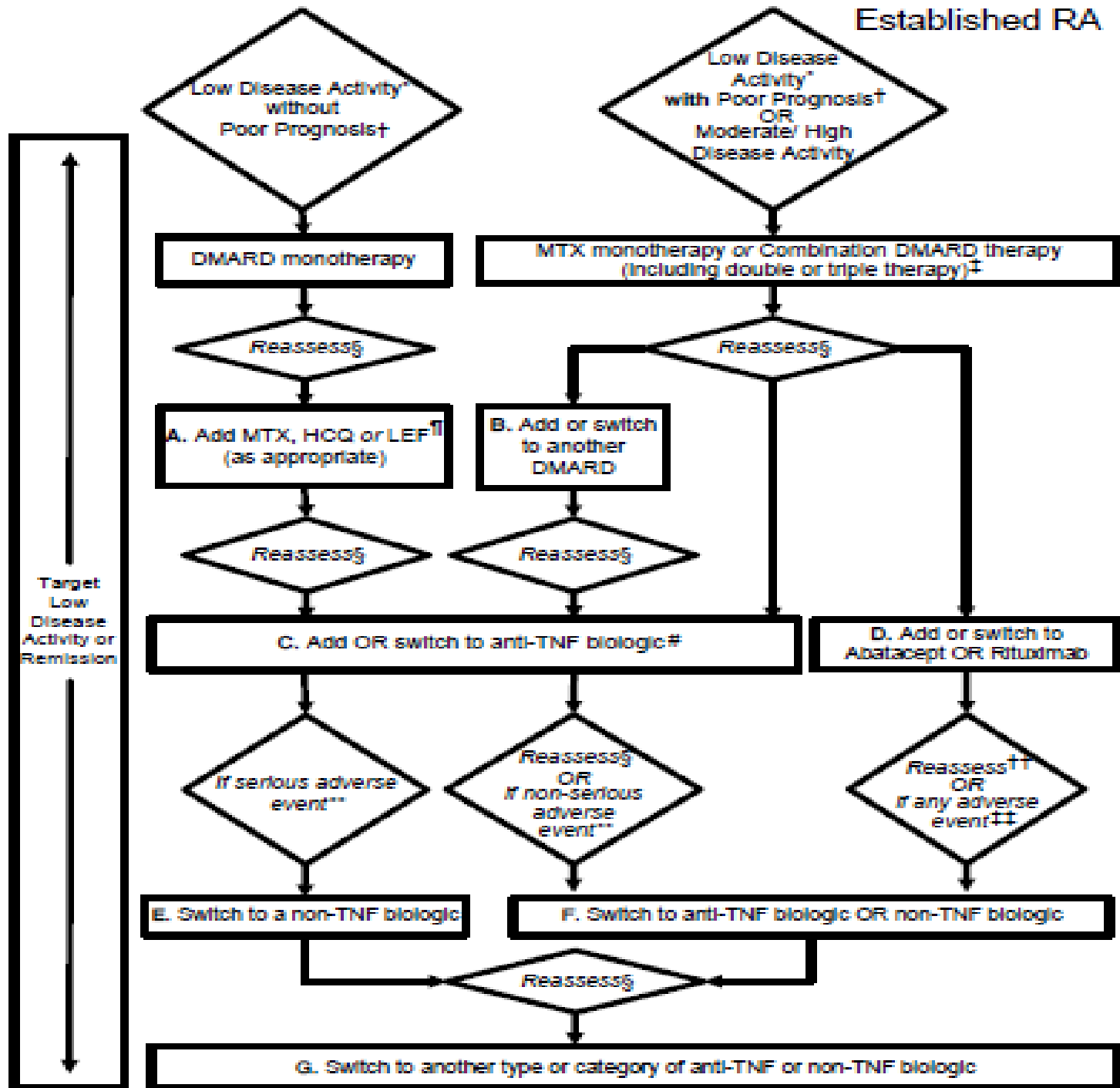
Agent	Usual dose/route	Side effects	Contraindications
<i>Infliximab</i> <i>(Anti-TNF)</i>	3 mg/kg i.v infusion at wks 0,2 and 6 followed by maintenance dosing every 8 wks Has to be combined with MTX.	Infusion reactions, increased risk of infection, reactivation of TB ,etc	Active infections,uncontrolled DM,surgery(with hold for 2 wks post op)
<i>Etanercept</i> <i>(Anti-TNF)</i>	25 mg s/c twice a wk May be given with MTX or as monotherapy.	Injection site reaction,URTI , reactivation of TB,development of ANA,exacerbation of demyelenating disease.	Active infections,uncontrolled DM,surgery(with hold for 2 wks post op)
<i>Adalimumab</i> <i>(Anti-TNF)</i>	40 mg s/c every 2 wks(fornightly) May be given with MTX or as monotherapy	Same as that of infliximab	Active infections

Agent	Usual dose/route	Side effects	Contraindications
Anakinra (<i>Anti-IL-1</i>)	100 mg s/c once daily May be given with MTX or as monotherapy.	Injection site pain, infections, neutropenia	Active infections
Abatacept (CTLA-4-IgG1 Fusion protein) Co-stimulation inhibitor	10 mg/ kg body wt. At 0, 2 , 4 wks & then 4wkly	Infections, infusion reactions	Active infection TB Concomitant with other anti-TNF- α
Rituximab (Anti CD20)	1000 mg iv at 0, 2, 24 wks	Infusion reactions Infections	Same as above
Tocilizumab (Anti IL-6)	4-8 mg/kg 8 mg/kg iv monthly	Infections, infusion reactions, dyslipidemia	Active infections

2012 ACR Update



Established RA



How to monitor Tt in RA?

- Disease activity is assessed by several parameters...
 - duration of morning stiffness, tender joint count, swollen joint count, observer global assessment, patient global assessment, visual analogue scale for pain, health assessment questionnaire, ESR, NSAID pill count, DAS score etc..
- Patient on MTX, SSZ or leflunamide show clinical improvement in 6-8 wks.
- Patient should be observed for 6 months before declaring a DMARD ineffective.

How long should Tt. be continued?

- Once remission is achieved , maintenance dose for long period is recommended.
- Relapse occurs in 3-5 months (1-2 months in case of MTX) if drug is discontinued in most instances.
- DMARDs are discontinued by patients because of **toxicity** or **secondary failure**(common after 1-2 yrs) and such patients might have to shift over different DMARDs over 5-10 yrs.
- Disease flare may require escalation of DMARD dose with short course of steroids.

Surgical Approaches

- Synovectomy is ordinarily not recommended for patients with rheumatoid arthritis, primarily because relief is only transient.
- However, an exception is synovectomy of the wrist, which is recommended if intense synovitis is persistent despite medical treatment over 6 to 12 months. Persistent synovitis involving the dorsal compartments of the wrist can lead to extensor tendon sheath rupture resulting in severe disability of hand function.
- Total joint arthroplasties , particularly of the knee, hip, wrist, and elbow, are highly successful.
- Other operations include release of nerve entrapments (e.g., carpal tunnel syndrome), arthroscopic procedures, and, occasionally, removal of a symptomatic rheumatoid nodule.

Thank you.