Integrated Teaching Program

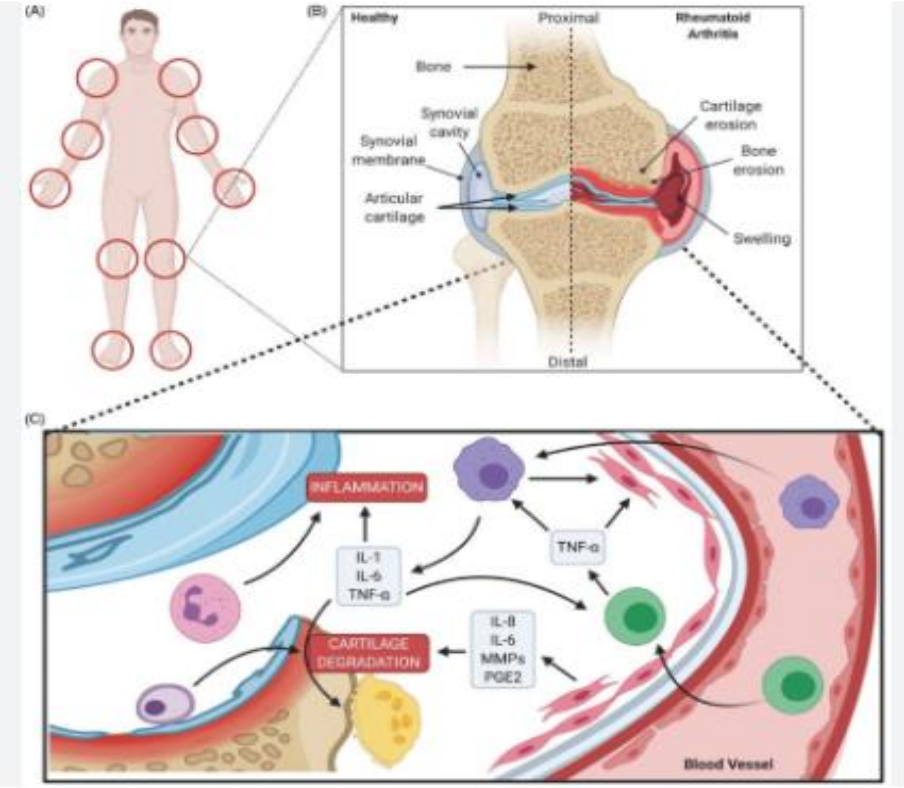
Rheumatoid Arthritis

Osteomyelitis

Rheumatoid Arthritis

Department of Microbiology
Department of Medicine
Department of Pharmacology

Immunopathogenesis of Rheumatoid Arthritis



Dr. Hasiba Mahmuda

Assistant Professor

Department of Microbiology

Bashundhara Ad-Din Medical College

Rheumatoid Arthritis(RA)

- Rheumatoid arthritis (RA) is an autoimmune, inflammatory disease.
- Occurs when immune system mistakenly attacks body’s own tissues, sp. joints.
- Characterized by clinical course of arthritis with exacerbations and remissions.
- Inflammation and pain in the joints occurs.

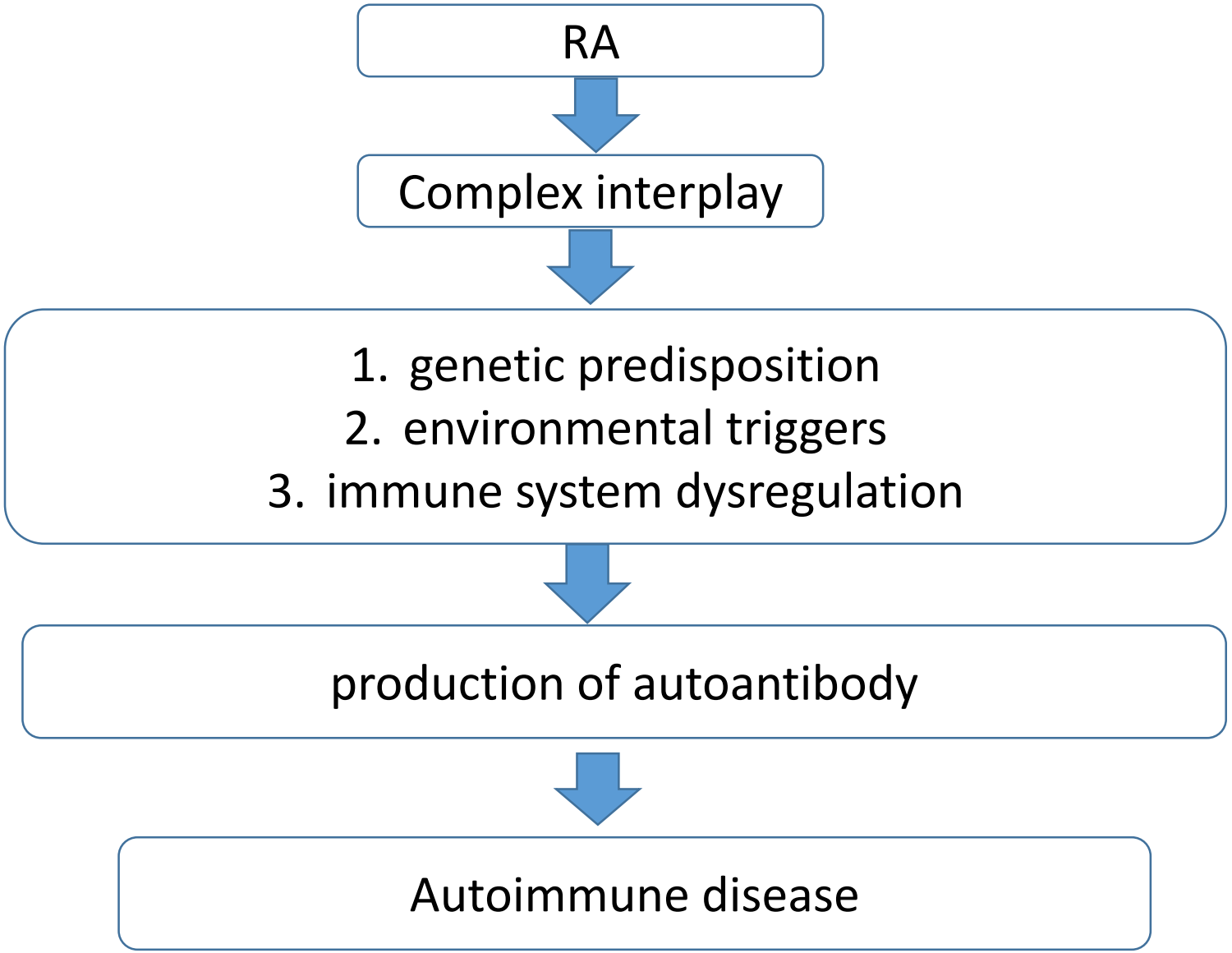
Major Immunological Features

- Presence of **Rheumatoid factors** (autoantibodies directed against the Fc portion of **IgG**) in serum and synovial fluid

- The involved synovium will contain-

❖Infiltration of lymphocytes and activated macrophages

❖ Local production of tumor necrosis factor-α & other proinflammatory cytokines


RA
Complex interplay
1. genetic predisposition
2. environmental triggers
3. immune system dysregulation
production of autoantibody
Autoimmune disease

Genetic Factors

- Inheritence of **HLA-DRB1 alleles** (DRB1*0101, DRB1*0401, DRB1*0404, DRB1*0405, DRB1*0408 etc,) increases the relative risk of RA

- **HLA-DRB1** polymorphism provides evidence that T cell recognition of antigen plays important role in pathogenesis of RA

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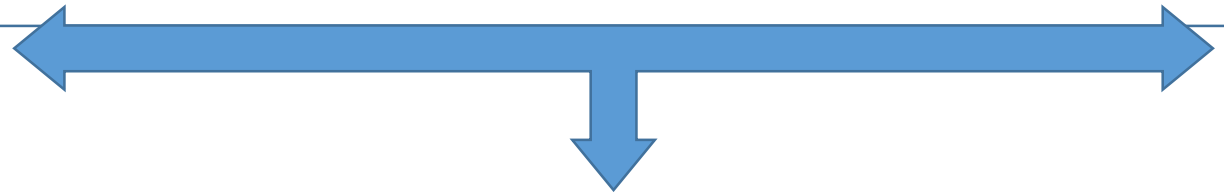
HLA DRB1 polymorphism with **SE(shared epitope) Allele**



Influence presentation of **arthritogenic Ags** to T cells	**Signal transduction** Ligand activating pathway leading to **inflammation & joint damage**	**Th17 polarization** is enhanced– autoimmunity occurs	**Gene dosage effect**: person with 2 HLA DRB1-associated alleles have higher risk of more severe RA	Associated with **high *ACPA positive RA**

***ACPA- Anti Citrullinated Protein Antibody**

Environmental Factors

Respiratory exposure: Smoking, vehicle & industrial pollution, Silica dust

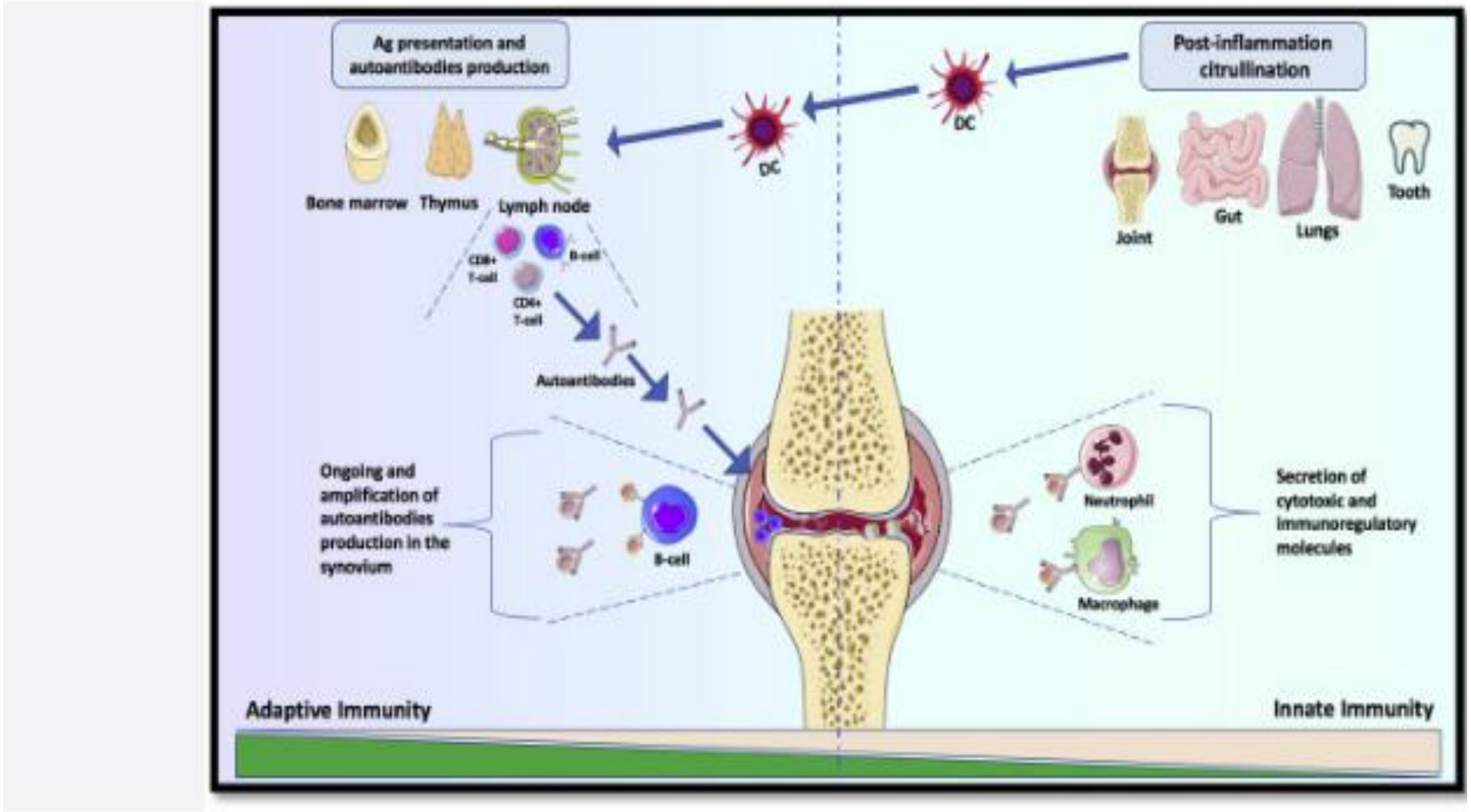
Sex specific: Female

Age: Postmenopause

Hormonal: Anti-estrogen treatment

Lifestyle habit: Obesity, Stress

Immune system dysregulation: Both innate & acquired



Immunologic pathogenesis

In a genetically susceptible individual, an environmental factor trigger autoimmune response by over activating **peptidylarginine deaminase (PAD) enzyme**

Conversion of **arginine** protein **into citrulline protein**

Production of **autoantibody**- primarily targeting ***citrullinated proteins**

Citrullin Proteins in joint tissue act as autoantigen

Triggering autoimmune response

Autoantibodies are formed- Rheumatiod factor (RA) & **Anti-Citrullinated Protein Antibodies (ACPA)**, ACPA is highly diagnostic in RA

***Immune complexes (IgG + Rheumatoid factor) fix complement: amplify inflammation**

Role of Innate immune cells in RA

- **Monocyte/macrophage**: Secret pro-inflammatory cytokines, release of metalloproteinases to destroy joints.

Activated macrophage- produce cytokine and chemokines- inflammation.

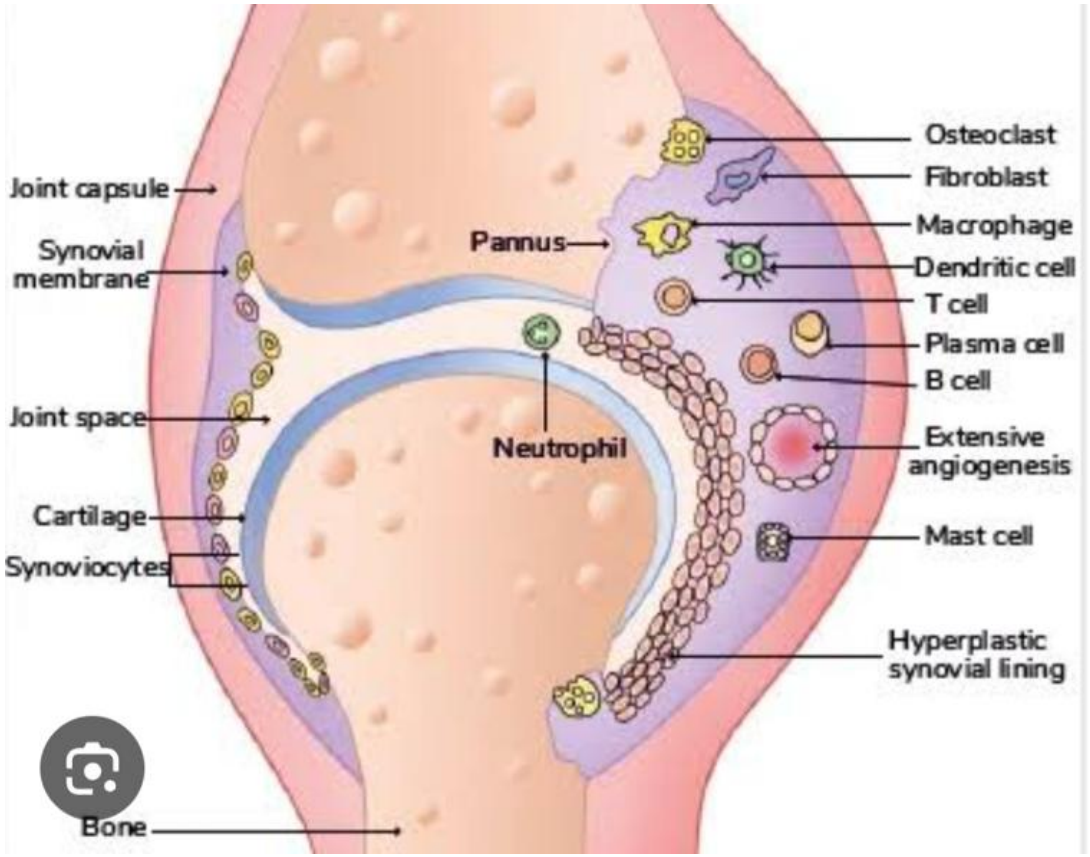
- **Dendritic cell**: Present autoantigens to autoreactive T & B cells, release pro-inflammatory cytokines.
- **Polymorphonuclear cell or neutrophil-** joint inflammation by releasing– PGs, proteolytic enzymes, reactive oxygen species, express PAD14 enzyme to make citrullinated proteins.
- **Natural killer cell**: Produce TNF, causing joint destruction, releasing Granzyme that creat new autoantigens and directly damage cartilage.

Role of Acquired Immune cells

- **T cell**: T cells activate macrophage & fibroblast—tissue destructive cell, Activate B cell to produce autoantibody
- **B cell**: Produce **RF & ACPA**, increasing the severity of RA,
- RF factor contributing to extra-articular disease,
- ACPA is specific for diagnosis of RA

Pathological changes occuring in joint with RA

- Inflammation
- Synovial thickening
- angiogenesis
- Pannus formation
- damage in joint
- bone erosion
- cartilage destruction



THANK YOU

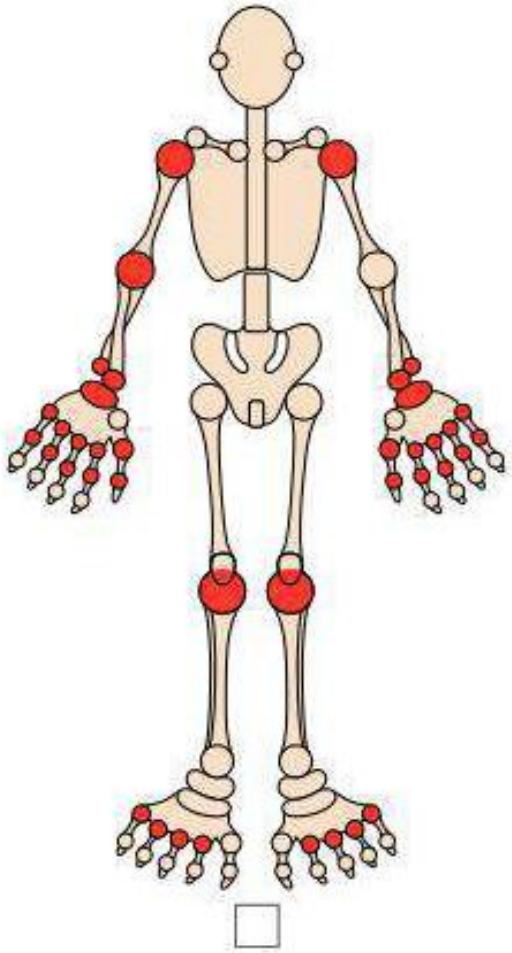
Rheumatoid Arthritis

Clinical features
Criteria
Investigations
Treatment
Complications

Dr. Jayanta Paul Chowdhury
Registrar, Medicine Department

Clinical features

- Age: 3rd to 5th decade.
- Sex: Male:Female = 1:3
- Symptoms:
  - Pain; joint swelling and stiffness of the small joints of the hands, feet and wrists(symmetrically)
  - Large joints such as wrists, elbows, shoulders, knees and ankles are also affected. In some cases, there may be monoarticular presentation.
  - The patient feels tired and unwell.
  - The pain and stiffness are significantly worse in the morning and may improve with gentle activity.



Rheumatoid arthritis typically targets the metacarpophalangeal and proximal interphalangeal joints of the hands and metatarsophalangeal joints of the feet as well as other joints in a symmetrical pattern.

Cont..

- Signs:

➤ The joints are usually warm, tender & swelled.

➤ There is limitation of movement.

➤ There may be muscle wasting.

- Deformities in advanced disease ---

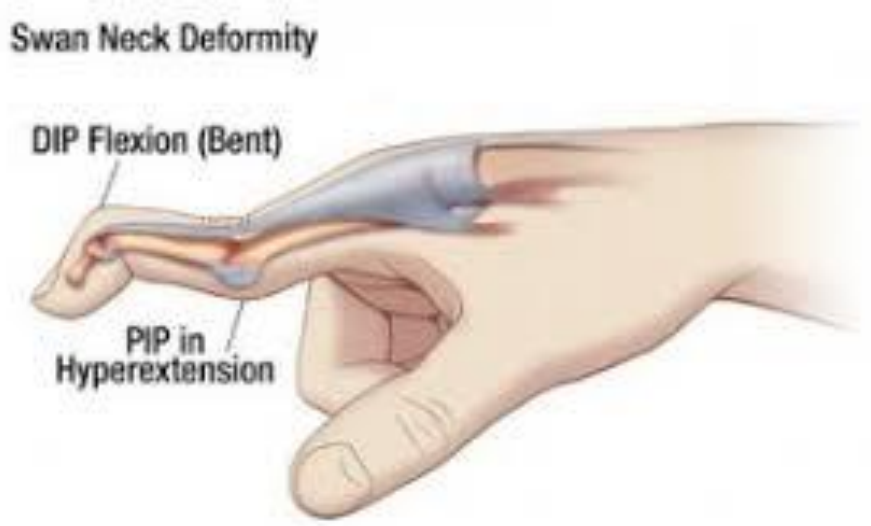
    Ulnar deviation.

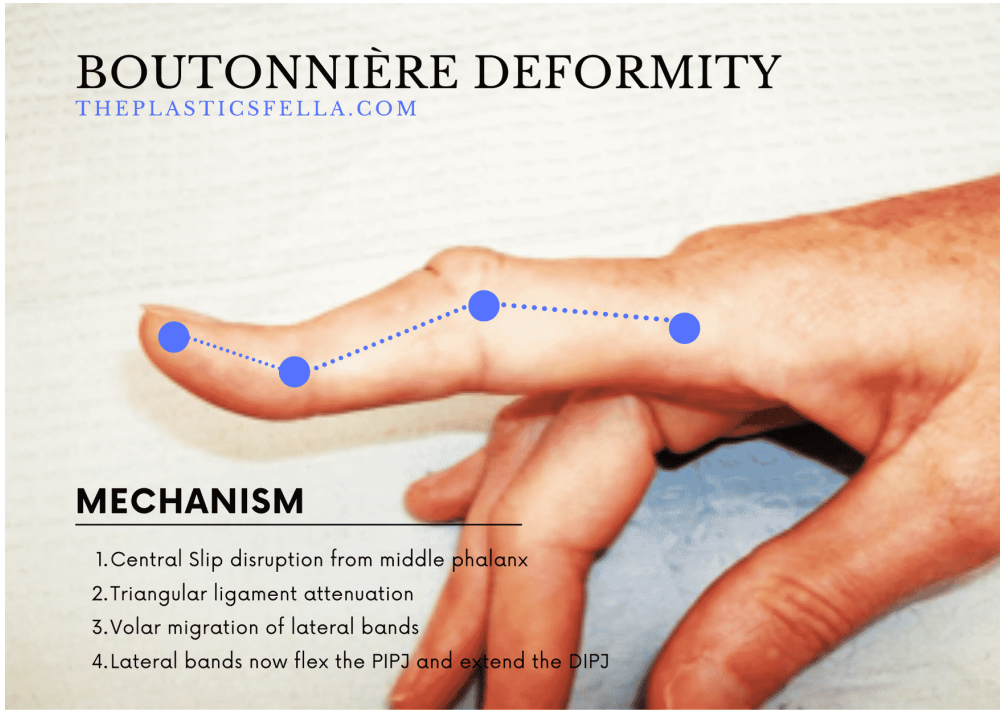
    'Swan-neck' deformity.

    'Z'-deformity of the thumb.

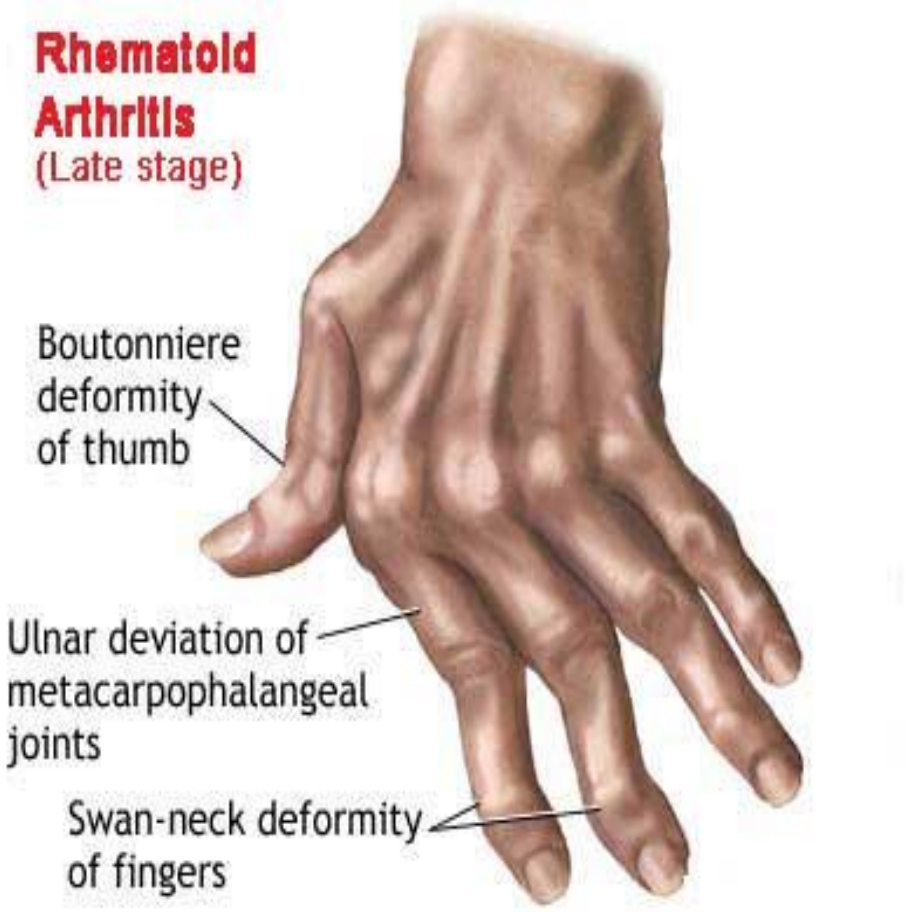
    Boutonniere deformity.

➤ Extra-articular features also develop

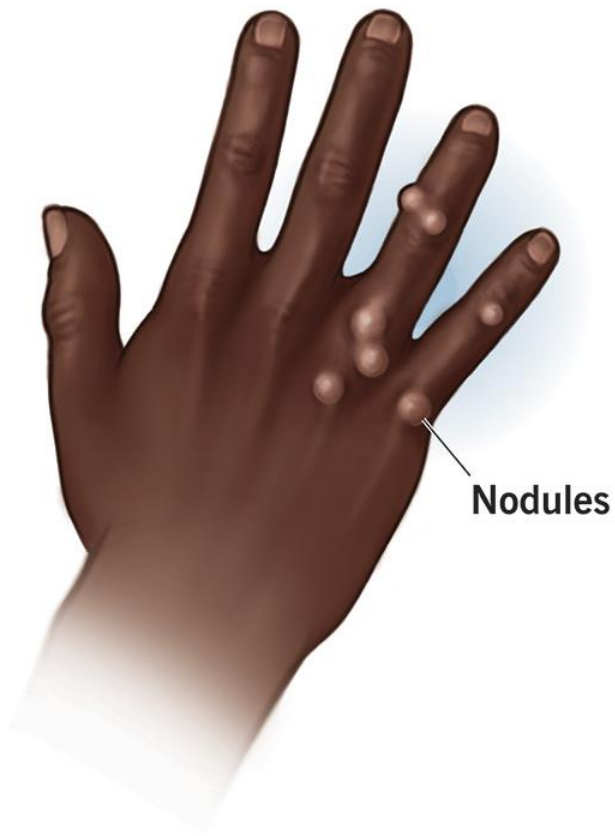




'Z'-deformity of the thumb



Rheumatoid nodules



26.53 Extra-articular manifestations of rheumatoid disease

Systemic

- Fever
- Weight loss
- Fatigue
- Susceptibility to infection

Musculoskeletal

- Muscle-wasting
- Tenosynovitis
- Bursitis
- Osteoporosis

Haematological

- Anaemia
- Thrombocytosis
- Eosinophilia

Lymphatic

- Felty syndrome (Box 26.54)
- Splenomegaly

Nodules

- Sinuses
- Fistulae

Ocular

- Episcleritis
- Scleritis
- Scleromalacia
- Keratoconjunctivitis sicca

Vasculitis

- Digital arteritis
- Ulcers
- Pyoderma gangrenosum
- Mononeuritis multiplex
- Visceral arteritis

Cardiac

- Pericarditis
- Myocarditis
- Endocarditis
- Conduction defects
- Coronary vasculitis
- Granulomatous aortitis

Pulmonary

- Nodules
- Pleural effusions
- Pulmonary fibrosis
- Obliterative bronchiolitis
- Caplan syndrome
- Bronchiectasis
- Pneumothorax

Neurological

- Cervical cord compression
- Compression neuropathies
- Peripheral neuropathy
- Mononeuritis multiplex

Amyloidosis

15.9 Criteria for diagnosis of rheumatoid arthritis*

Criterion	Score
Joints affected	
1 large joint	0
2–10 large joints	1
1–3 small joints	2
4–10 small joints	5
Serology	
Negative RF and ACPA	0
Low positive RF or ACPA	2
High positive RF or ACPA	3
Duration of symptoms	
<6 wks	0
>6 wks	1
Acute phase reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

Patients with a score ≥6 are considered to have definite RA.

*European League Against Rheumatism/American College of Rheumatology 2010 Criteria.
(ACPA = anti-citrullinated peptide antibodies; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor)

26.55 Investigations and monitoring of rheumatoid arthritis

To establish diagnosis

- Clinical criteria
- Erythrocyte sedimentation rate and C-reactive protein
- Ultrasound or magnetic resonance imaging
- Rheumatoid factor and anti-citrullinated peptide antibodies

To monitor disease activity and drug efficacy

- Pain (visual analogue scale)
- Early morning stiffness (minutes)
- Joint tenderness
- Joint swelling
- DAS28 (Fig. 26.37)
- Erythrocyte sedimentation rate and C-reactive protein

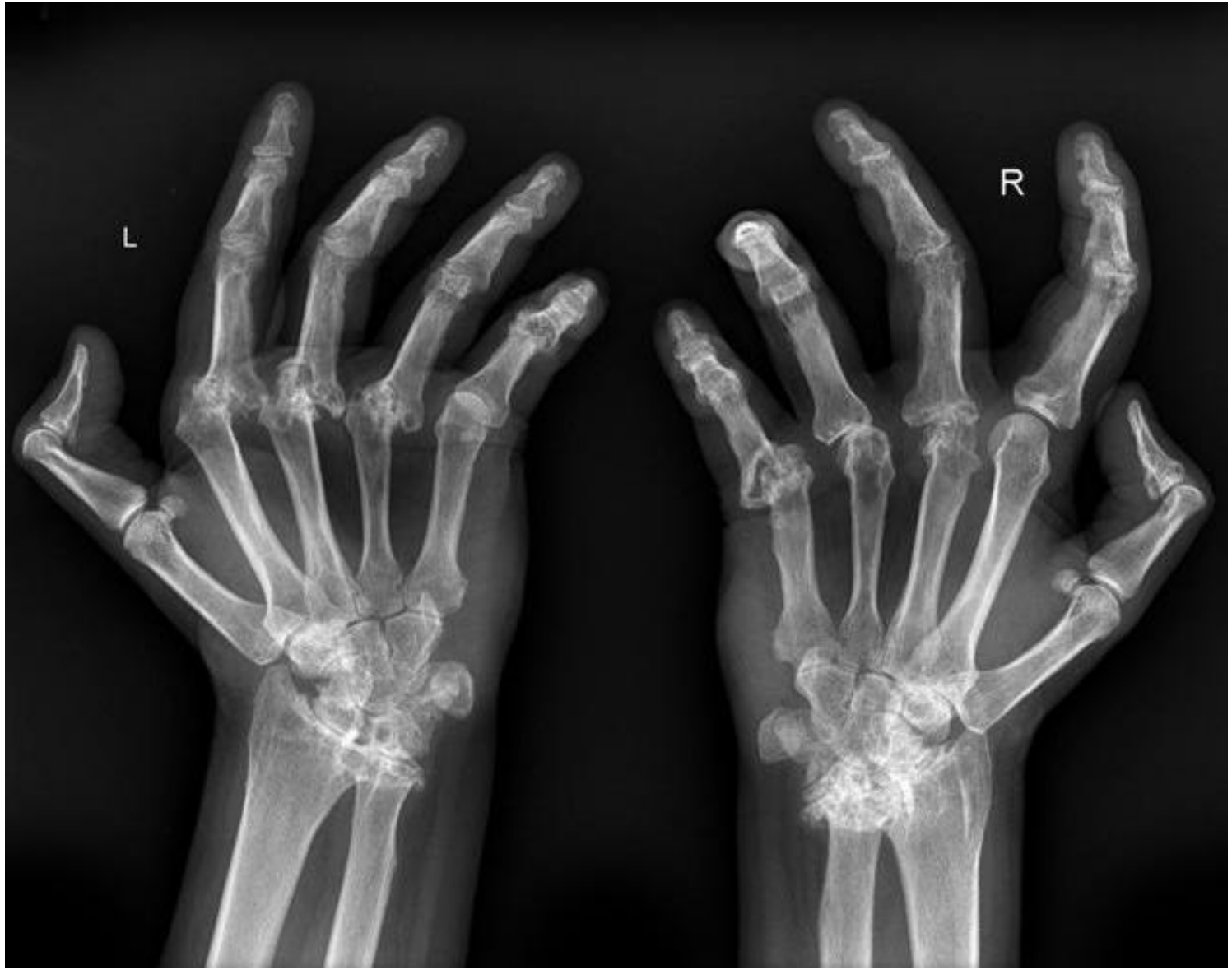
To monitor disease damage

- X-rays
- Functional assessment

To monitor drug safety

- Urinalysis
- Full blood count
- Chest X-ray
- Urea and creatinine
- Liver function tests

Xray of
Rheumatoid Arthritis



Treatment

- **Non-pharmacological therapy** –
  - **Patient Education** .
  - **Rest** and splinting. This is necessary where practical for any acute flare-up of arthritis.
  - **Exercise**. It is important to have regular exercise, especially walking and swimming. Have hydrotherapy in heated pools.
  - **Smoking cessation**. This is strongly recommended.
  - **Joint movement**. Each affected joint should be put daily through a full range of motion to keep it mobile and reduce stiffness.

Cont…

❑**Drug therapy**:

➤NSAIDs.

➤ Classical DMARDs: Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide.

➤ Targeted Synthetic DMARDs : Tofacitinib, Baricitinib, Filgotinib, Upadacitinib

➤ Corticosteroid: For induction of remission.

Cont…

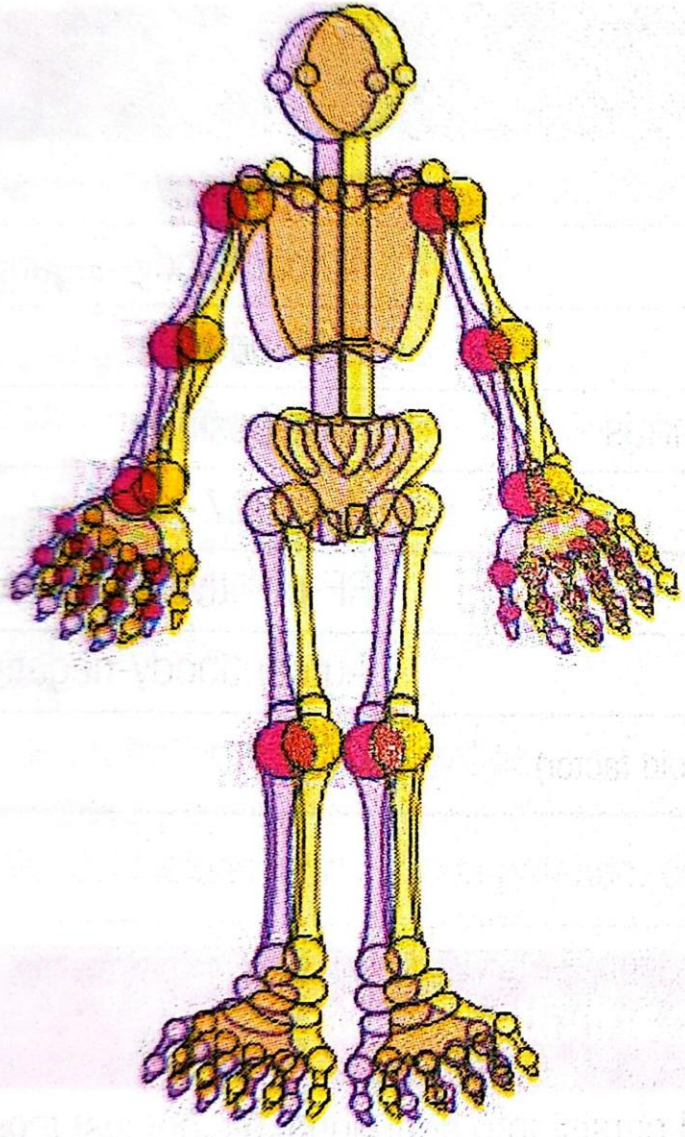
- **Biological drugs (*monoclonal antibodies*) used in the treatment of RA**:
  - Anti-TNF therapy: Etanercept, Infliximab, Adalimumab.
  - Anti-B cell therapy: Rituximab.
  - Inhibitor of T-cell activation: Abatacept.
  - Anti-IL6: Tocilizumab.
  - Anti-IL17 : Secukinumab
  - Anti-IL1 : Anakinra

Cont…

- **Surgery:**

✓Synovectomy of the wrist or finger tendon sheaths of the hands may be required.

✓In later stages of the disease: Osteotomy, arthrodesis, arthroplasties



Calculation

- Count swollen joints
- Count tender joints
- Measure erythrocyte sedimentation rate*
- Note patient global health assessment (1–100)
- Enter data into calculator: www.4s-dawn.com/das28

Interpretation

• > 5.1	High activity
• ≥ 3.2–5.1	Moderate activity
• 2.6–3.2	Low disease activity
< 2.6	Remission

Fig. 26.37 Calculation of the Disease Activity Score 28 (DAS28).
*Erythrocyte sedimentation rate or C-reactive protein can be used for the calculation.

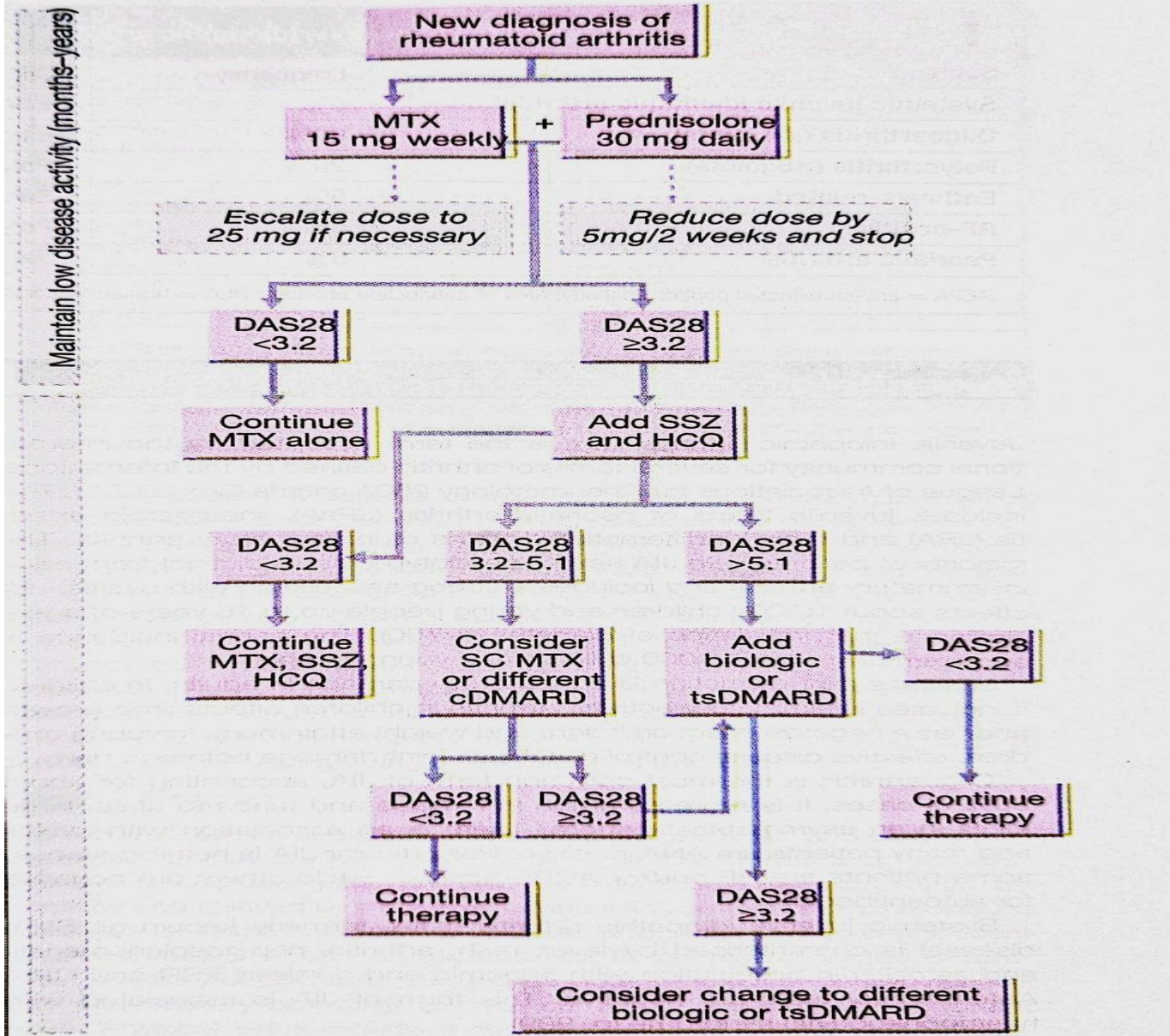


Fig. 26.38 **Algorithm for the management of rheumatoid arthritis.**
(DAS28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; MTX = methotrexate; SSZ = sulfasalazine; ts = targeted synthetic; SC = subcutaneous)

Remission Criteria of RA

Table 1. American College of Rheumatology preliminary criteria (1) for remission of rheumatoid arthritis (RA)*

A minimum of 5 of the following for at least 2 consecutive months:

- Morning stiffness not to exceed 15 minutes
- No fatigue
- No joint pain
- No joint tenderness or pain on motion
- No soft tissue swelling in joints or tendon sheaths
- ESR (Westergren method) <30 mm/hour (women) or 20 mm/hour (men)

* Exclusions prohibiting a designation for complete clinic remission: clinical manifestations of vasculitis, pericarditis, pleuritis, myositis, unexplained recent weight loss, or fever secondary to RA. ESR = erythrocyte sedimentation rate.

Complications of Rheumatoid arthritis:

1) Joint deformity.
2) Disability.
3) Tendon rupture.
4) Bursitis.
5) Osteoporosis.
6) Muscle wasting.
7) Scleritis & episcleritis.
8) Pericarditis, myocarditis, endocarditis.
9) Pleural effusion.
10) Fibrosing alveolitis.
11) Susceptibility to infection.
12) Vasculitis.
13) Cervical cord compression.
14) Peripheral neuropathy.
15) Sub-luxation of atlanto-axial joint

References-

- Davidson's Principles and Practice of Medicine 24th Edition.

- John Murtagh's General Practice 8th Edition.

THANK YOU

Pharmacological Intervention in RA

Dr. Sagia Afrose
Associate Professor
Department of Pharmacology
Bashundhara Ad-din Medical College

Pharmacological Management

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroid
- Disease modifying anti-rheumatic drugs (DMARDs)
  - Classical DMARD (cDMARD)
  - Biologic DMARD (Biologics)
  - Targeted synthetic DMARD (tsDMARD)/ Jenus kinase inhibitor

Routes of administration

- NSAID : Oral, IV, IM
- Corticosteroid : Oral, IV, Intramuscular , Intra-articular
- Classical DMARDs : Oral, SC
- Targeted Synthetic DMARDs : Oral
- Biologics : IV, SC

NSAIDs

- Used in RA only for symptom control
- Reduce pain and swelling by inhibiting COX
- Do not alter course of the disease.
- Chronic use should be minimized to avoid adverse effects

26.29 Commonly used NSAIDs and their risk of gastrointestinal bleeding and perforation

Drug	Daily adult dose	Doses/day	Idiosyncratic side-effects, comments
Low risk			
Celecoxib	100–200 mg	1–2	Selective COX-2 inhibitor
Etoricoxib	60–120 mg	1	Selective COX-2 inhibitor
Medium risk			
Ibuprofen	1600–2400 mg	3–4	Gastrointestinal adverse effects more likely than with COX-2 inhibitors, even with PPI therapy
Naproxen	500–1000 mg	1–2	
Diclofenac	75–150 mg	2–3	
High risk			
Indometacin	50–-200 mg	3–4	High incidence of dyspepsia and CNS side-effects

(CNS = central nervous system; COX = cyclo-oxygenase; PPI = proton pump inhibitor)

Common adverse effects of NSAIDs

- **Gastrointestinal**: Stomach ulcers, bleeding, perforation, abdominal pain, heart burn
- **CVS**: Heart attack, hypertension, and increased risk of thromboembolic events
- **Renal**: Kidney damage, decreased kidney function and edema
- Increase risk of stroke
- Aggravation of Asthma
- **Hepatotoxicity**

Recommendations for the use of NSAIDs

- Use lowest dose for shortest period of time to control symptoms
- Avoid NSAIDs in patients on warfarin & cardiovascular disease
- Never prescribe more than one NSAID at a time
- Co-prescribe a proton pump inhibitor for patient with risk factors for gastrointestinal adverse effects
- Allow 2-3 weeks to asses efficacy. If response is inadequate consider another NSAIDs

Corticosteroids

Commonly used

- Prednisone
- Methyl-prednisolone
- Hydrocortisone

Role of Corticosteroids :

- Provide potent **anti-inflammatory effects ,** relief symptoms during acute flare-ups
- As **bridge therapy** for 6-8 weeks before the action of DMARDs begins
- **Modify disease progression,** prevent joint damage, bony erosions in the early stage
- **Intra-articular** injection into affected joints, provide targeted & long-lasting pain relief

Potential Side Effects:

- Weight gain
- Increase blood sugar levels
- Hypertension
- PUD
- delayed wound healing
- Increased Risk of Infections
- Osteoporosis
- Mood swings, anxiety or depression.

Disease modifying anti-rheumatic drugs/DMARDs

- Drugs that actually alter the disease course by slowing down the progression of disease
- Should be used as soon as diagnosis is confirmed

Classical DMARDs

More commonly used

- ✓Methotrexate
- ✓Sulfasalazine
- ✓Hydroxychloroquine
- ✓Leflunomide

Less commonly used

- ✓Azathioprine
- ✓Cyclophosphamide
- ✓Cyclosporine A
- ✓Mycophenolate mofetil

Selection of DMARDs

- There is no strict guideline for drug selection
- MTX is the commonly used cDMARD

Mechanism of action of MTX

1. **Antifolate effect:** Inhibit Dihydrofolate Reductase decrease folate levels which is essential for DNA synthesis and cell proliferation.

So Folic acid must be co-prescribed along with MTX

2. **Anti-inflammatory Effects**: reduces the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukins (IL-1, IL-6), and others. This helps decrease inflammation in the joints.

DMARDs alone or in combination

- Single use of MTX is modestly effective

- But it is often used in combination with other DMARDs or biologics to enhance effectiveness in severe cases

cDMARDs with adverse effects

Drug	Maintenance Dose	Regular Monitoring			Side effects
		FBC	LFT	Other	
Methotrexate	15-25mg P/O wkly	✔	✔	-	Nausea, vomiting, Diarrhoea, Mouth ulcer, hepatotoxicity, pneumonitis, Marrow suppression, alopecia
Sulfasalzine	2-4 g P/O daily	✔	✔	-	Hepatitis, neutropenia
Hydroxychloro-quine	200-400mg P/O daily	-	-	Visual function	Corneal deposits, retinopathy , diarrhoea, headache
Leflunomide	10-20 mg P/O daily	✔	✔	BP	Alopecia, hepatitis, HTN
Azathioprine	1-2.5mg/kg P/O daily	✔	✔	-	Marrow suppression
Ciclosporin	3-5 mg/kg P/O daily	-	-	BP, eGFR	Renal insufficiency, HTN

Limitations of Classical DMARDs

- Delayed onset of action
- lose efficacy with time
- Common side effects : gastrointestinal effects, hepatotoxicity, renal impairment, marrow suppression, hypertension, retinopathy
- Prolong use may cause increase susceptibility to infection
- Requires regular monitoring of LFT, KFT, blood cell count, BP, GFR , visual function

Targeted synthetic DMARDs

- Typically used when cDMARD are not effective or cause intolerable side effects
- Works by blocking specific enzyme, pathway or receptor involved in the inflammatory response
- Most well-known class within tsDMARDs are Janus kinase inhibitor
- JAK inhibitors : Tofacitinib, Baricitinib, Upadicitinib
- Can be administered orally

Targeted synthetic DMARDs

Drug	Maintenance Dose	Regular Monitoring			Indications
		FBC	LFT	Other	
Apremilast	30mg BD	-	-	-	PsA
Tofacitinib	5mg BD	✔	✔	Infection	RA
Baricitinib	2-4 mg OD	-	-	Infection	RA, PsA
Upadacitinib	15-30mg OD	-	-	Infection	RA
Filgotinib	200mg OD	-	-	Infection	RA, PsA, axSpA

Mechanism of action of JAK inhibitors

- JAK inhibitors works by blocking the activity of one or more janus kinase enzymes which are involved in the signaling pathways of various cytokines and growth factors.
- These enzymes play a key roles in the immune system and in inflammation.

Common Side Effects

1. Infections: Upper RTI, UTI, Herpes zoster, Pneumonia
2. Gastrointestinal: Nausea, diarrhea, abdominal pain
3. Elevated liver enzymes
4. Elevated cholesterol levels
5. Skin reactions: Rashes, acne, skin irritation

Biologic DMARDs in RA

- They are monoclonal antibodies derived from living organism, plant or animal

- used to treat moderate to severe rheumatoid arthritis that has not responded adequately to other treatments

Biologic DMARDs

- TNF α blocking agents : Infliximab, Adalimumab, Golimumab, Certolizumab, Etanercept
- T cell inhibitor : Abatacept
- CD20 antagonist /(B-cell depletor) : Rituximab
- Anti-IL-6 receptor antibody : Tocilizumab

Mechanism of action

- Newer drugs that target specific molecule involve in immune response, including cytokines, immune cells, and signaling pathways, to reduce inflammation and prevent joint damage in autoimmune diseases.
- highly specific for its function and target antigen
- Their precise targeting of immune mechanisms helps them to be highly effective in controlling disease progression

Limitations

- Very expensive
- usually **given by IV Injection/ infusion**
- require a **strict follow-up schedule**
- All biologics increase **risk of infection**

- Patients should be screened for tuberculosis and other infections before starting a biologic

Biologic DMARDs

Drug	Maintenance Dose	Side effects
Infliximab	3-5mg/kg IV every 8wkly	Mild infection, infusion reaction
Adalimumab	40mg S/C 2wkly	Upper RTI, worsen demylinating syndrome
Etanercept	50mg S/C wkly	Headache, lupus like syndrome
Rituximab	2×1gm I/V 2wks apart	Fever, dyspnea, angioedema
Abatacept	125mg S/C wkly	Nasopharyngitis, diarrhoea, pyrexia
Toclizumab	162mg S/C wkly	Neutropenia, elevated liver enzymes
Certolizumab	200mg S/C 2wkly	Pyrexia, fatigue, arthralgia
Golimumab	50mg S/C 4wkly	Photosensitivity, optic neuritis

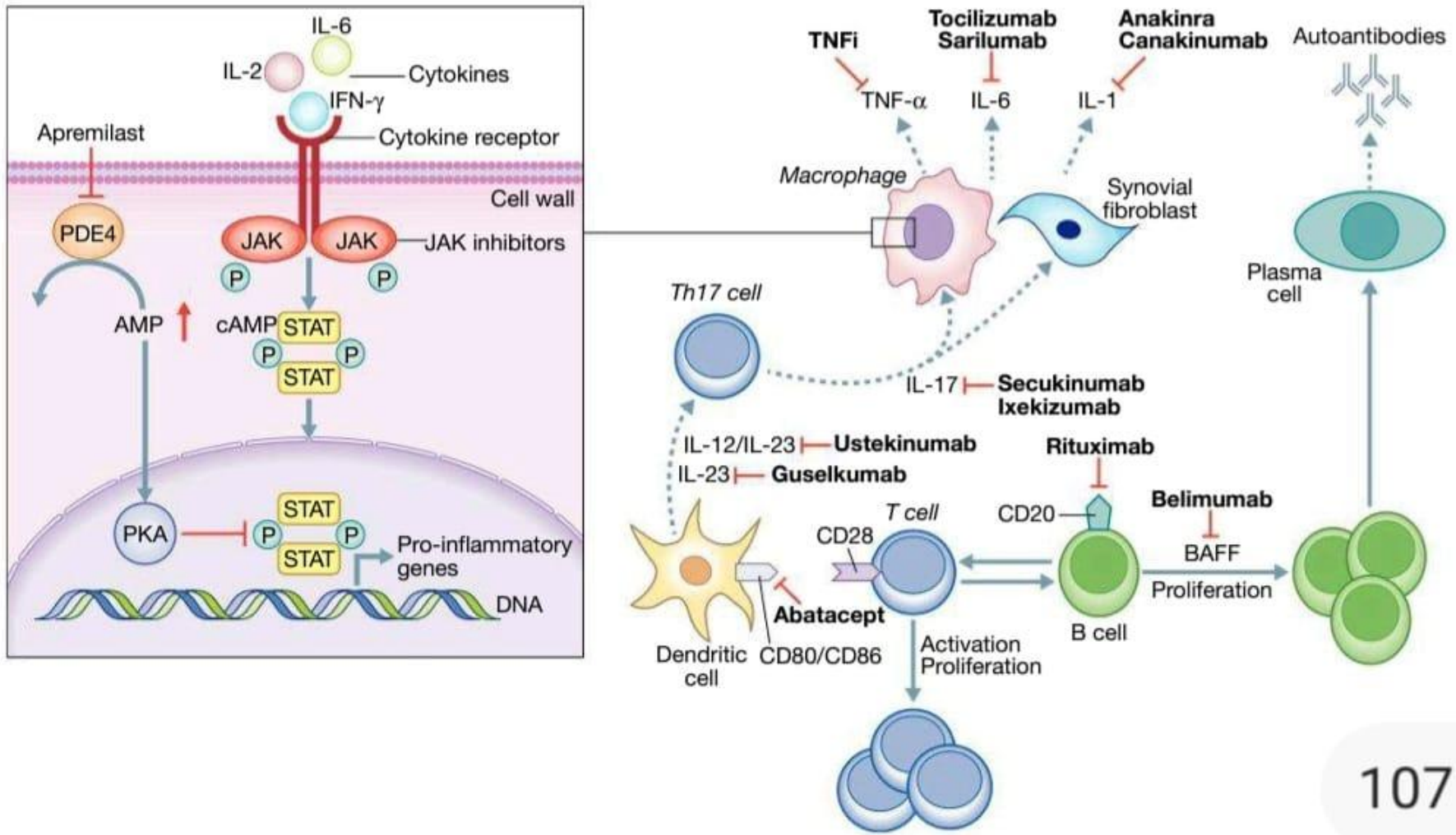


Fig. 26.15 Targets for biologic therapies in inflammatory rheumatic diseases. Biologic treatments for inflammatory rheumatic diseases work by targeting key cytokines and other molecules involved in regulating the immune response. (BAFF = B-cell-activating factor of the TNF family; AMP = adenosine monophosphate; cAMP = cyclic AMP; CD = cluster of differentiation; IL = interleukin; JAK = Janus activated kinase; P = phosphate; PDE = phosphodiesterase; PKA = protein kinase A; STAT = signal transducers and activators of transcription; TNF-α = tumour necrosis factor alpha; TNFi = inhibitor of tumour necrosis factor)

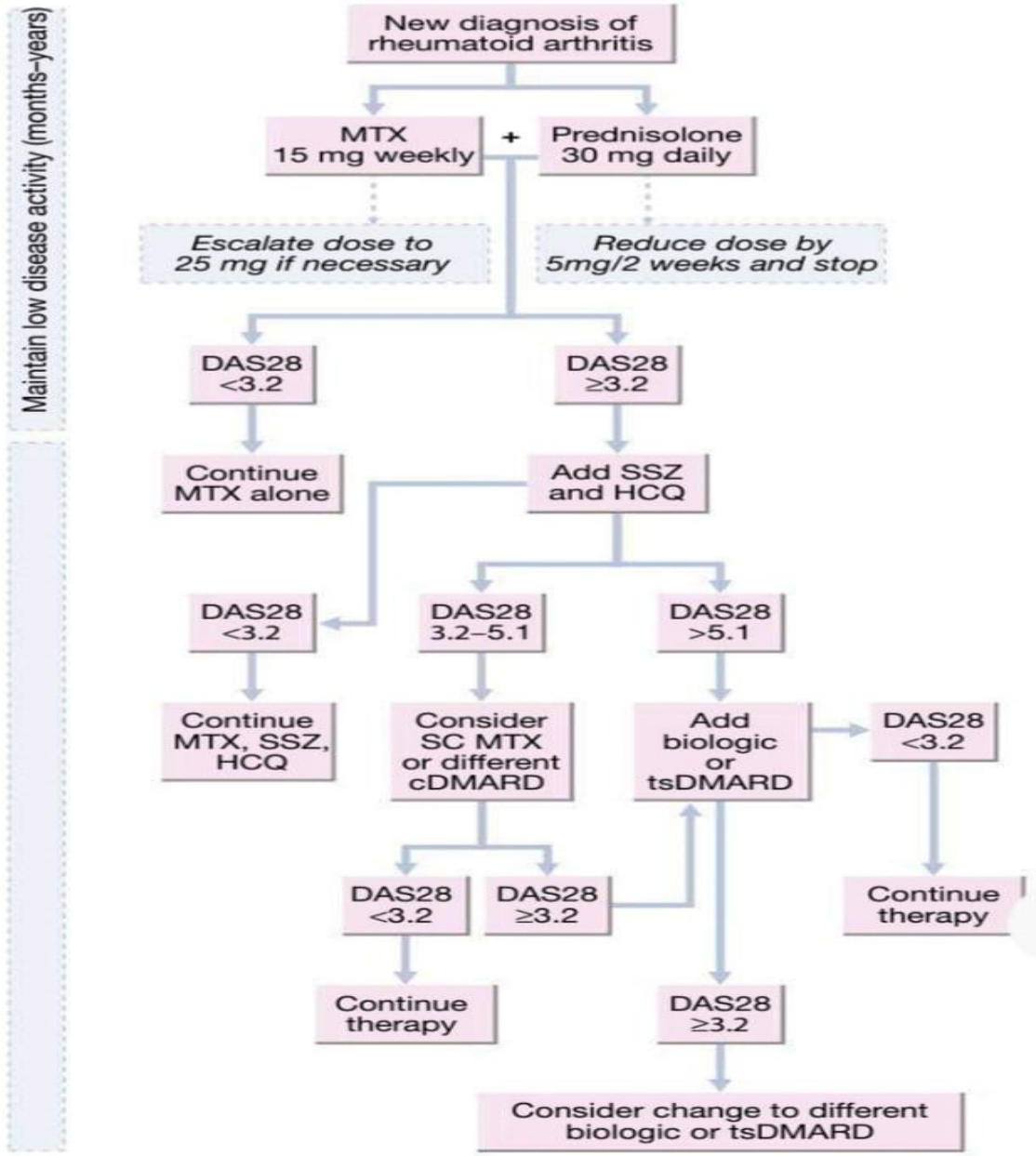


Fig. 26.38 Algorithm for the management of rheumatoid arthritis.
(DAS28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; MTX = methotrexate; SSZ = sulfasalazine; ts = targeted synthetic; SC = subcutaneous)

RA in pregnancy

- Paracetamol is the oral analgesic of choice
- Corticosteroids may be used to control disease flare
- Methotrexate and leflunomide should be discontinued for at least 3 months before trying to conceive.
- DMARDs used: sulfasalazine, hydroxychloroquine, azathioprine or cyclosporin if required to control inflammation.
- DMARDS avioded: Methotrexate, Leflunomide, Cyclophosphamide
- Biological therapies: Safety during pregnancy is currently unclear.

Thank You