APPROACH TO THE TREATMENT OF INFLAMMATORY POLYARTHRITIS

DR.AFSAR SAYEEDA

FRCP

CONSULTANT INTERNIST & RHEUMATOLOGIST

HEAD, CLINICAL TEACHING UNIT .

KING KHALID UNIVERSITY HOSPITAL

KSUMC, RIYADH, KSA .

CAUSES OF INFLAMMATORY POLYARTHRITIS

- **INFECTIONS - VIRAL/ BACTERIAL** (H PARVOVIRUS B19, CMV,CSV.HEPB.HIV,EBV,MUMPS,VZV ,ADENO.ENTERO.HHV)
- STAPH AUREUS, GONORRHOEA,GRAM NEGATIVE BACILLI
- **DIRECT/INDIRECT(REACTIVE ARTHRITIS-**SHIGELLA,SALMONELLA,CHLAMYDIA, YERSINIA,CAMPYLOBACTER,GROUP A STREPTOCOCCI, TROPHEREMA WHIPPELI ,WHIPPLES, INFECTIVE ENDOCARDITIS)

- **SYSTEMIC RHEUMATIC DISEASE –RA/SLE/AOSD/JRA**
- **CRYSTAL INDUCED ARTHRITIS -Gout / Pseudogout**
- **SYSTEMIC VASCULITIDES –HSP/PAN/WG**
- **SERONEGATIVE SPONDYLOARTHROPATHEIS - Psoriatic arthritis ,**
  IBD related (enteropathic) ,
  Reactive arthritis &
  Ankylosing Spondylitis

INFLAMMATORY VS NONINFLAMMATORY

INFLAMMATORY

- MORNING STIFFNESS OF MORE THAN AN HOUR
- LOW GRADE TEMPERATURE, FATIGUE, SKIN RASH
- SIGNS OF INFLAMMATION- RUBOR (REDNESS)
- WARMTH(CALOR). SWELLING(EFFUSION-TUMOUR), TENDERNESS(DOLOR) LOSS OF FUNCTION.
- LABS –ESR, CRP ,ANAEMIA OF CHRONIC DISEASE, RF, ANTICCP, ANA….
- X RAYS- EROSIONS, UNIFORM JOINT SPACE NARROWING.
- SYNOVIAL FLUID ANALYSIS -> 2000(NONINFECTIOUS), > 50000(INFECTIOUS)PREDOMINANTLY NEUTROPHILS.

NONINFLAMMATORY

- LESS THAN AN HOUR
- BONY PROLIFERATION – HEBERDENS NODES, BOUCHARDS NODES)
- NORMAL LABS
- JOINT SPACE NARROWING, SUBCHONDRAL SCLEROSIS,OSTEOPHYTES .
- SYNOVIAL FLUID < 200 CELLS 50% NEUTROPHILS

RHEUMATOID ARTHRITIS

- ACUTE AND CHRONIC INFLAMMATION IN SYNOVIUM CAUSING PROLIFERATION AND DESTRUCTION OF JOINT TISSUES.

- TO ACHIEVE THE BENEFITS OF INTERVENTION WITH EARLY DMARDS DEPENDS THE DIAGNOSIS OF RA AS EARLY AS POSSIBLE.

- RECOGNISE RA EARLY BEFORE IRREVERSIBLE JOINT INJURY OCCURS.

THE GOALS OF RA TREATMENT ARE TO:

- STOP INFLAMMATION(PUT DISEASE IN REMISION)
- RELEIVE SYMPTOMS
- PREVENT JOINT AND ORGAN DAMAGE
- IMPROVE PHYSICAL FUNCTION AND OVERALL WELLBEING
- REDUCE LONG TERM COMPLICATIONS

NONPHARMACOLOGIC THERAPIES

- **PATIENT EDUCATION**
- **REST,EXERCISE,PHYSICAL AND OCCUPATIONAL THERAPY**
- **NUTRITIONAL AND DIETARY COUNSELLING**
- **INTERVENTIONS TO DECREASE THE CV RISKS, eg: SMOKING CESSATION**
- **IMMUNISATIONS TO DECREASE THE INFECTIOUS COMPLICATIONS OF IMMUNOSUPPRESSIVE THERAPIES.**

Pretreatment evaluation

Prior to starting, resuming, or significantly increasing therapy with nonbiologic or biologic DMARDs, we do the following baseline studies :

- General testing for all patients —CBC, s. creatinine, AT, ESR, & CRP .
- Serologic testing for hepatitis prior to **methotrexate , leflunomide** , or biologic DMARDs — (*All patients at increased risk of hepatitis, such as those who have a history of iv drug abuse, multiple sex partners in the previous 6 mnths, and those who are healthcare workers, should be screened for hepatitis B and C before starting these medications)*
- Ophthalmologic screening for **hydroxychloroquine** use .
- Testing for latent tuberculosis —skin testing or an interferon-gamma release assay prior to all biologic DMARDs and prior to use of the Janus kinase inhibitor, **tofacitinib**.

Choice of therapy

- Rapidly acting antiinflammatory medications, including nonsteroidal antiinflammatory drugs (**NSAIDs**) and systemic and intraarticular **glucocorticoids**.
- **Nonbiologic DMARDs** : hydroxychloroquine , sulfasalazine , methotrexate , and leflunomide .
- **Biologic DMARDs:** produced by *recombinant DNA technology*, generally *target cytokines or their receptors* or are directed against other cell surface molecules.
- **Several kinase inhibitors** : **Tofacitinib** . It is an orally administered small molecule DMARD that inhibits cytokine and growth factor signalling *through interference with Janus kinases.*
- **Denosumab** in Osteoporosis

Note: Ruxolitinib is used in Polycythemia Vera

Table 1. Summary of Nonbiological DMARDs for Rheumatoid Arthritis

Drug	Usual Maintenance Dosage	Approximate Time for Benefit
Azathioprine	1-2.5 mg/kg/day divided over 2-4 doses. After 4 wk, may increase by 0.5 mg/kg/day every 4 wk	2-3 mo
D-penicillamine	250-750 mg/day	3-6 mo
Gold	Oral: 3 mg twice daily IM: 25-50 mg every 2-4 wk	4-6 mo 3-6 mo
Hydroxychloroquine	200 mg twice daily	2-6 mo
Leflunomide	100 mg daily for 3 days then 20 mg per day	4-12 wk
Methotrexate	Oral/injectable: 7.5-20 mg/wk	1-2 mo
Sulfasalazine	1,000 mg 2-3 times daily	1-3 mo

IM: intramuscular; DMARDs: disease-modifying antirheumatic drugs.
Source: References 10, 14.

NonBiologic DMARDs

Names	Major Adverse effect
Hydroxychloroquine	damage to the retina of the eye
Sulfasalazine	nausea, vomiting, loss of appetite, headache, dizziness, may cause skin and urine to turn orange-yellow.
methotrexate	Rash, liver/lung/ bone marrow toxicity
Leflunomide	Diarrhea
Azathioprine	nausea, vomiting, decreased appetite, liver function abnormalities, low white blood cell counts
Cyclosporine	HTN, Renal dysfunction

Biologic DMARDs

Names	Examples
TNF Inhibitor	Etanercept, Golimumab, Adalimumab and Certolizumab, Infliximab (E-GACI)
IL1 Antagonist	Anakinra
IL-6 receptor antagonist	Tocilizumab
T-cell costimulation blocker	Abatacept
Anti-CD20 B-cell depleting monoclonal antibody	Rituximab

Early use of DMARDs : stratification

mildly active RA
moderately to severely active RA,
resistant to initial DMARD therapy (eg, MTX)

DEFINITION OF MILDLY ACTIVE RA

Patients with mildly active rheumatoid arthritis (RA) typically meet *ACR/EULAR criteria for RA* and have all of the following

1. Fewer than five inflamed joints
2. Mildly elevated or normal ESR and C-rp levels
3. No extraarticular disease
4. No evidence of erosions/cartilage loss on radiographs of the hands, wrists, and feet
5. Low levels of measures of disease activity such as the DAS28

DEFINITION OF MODERATELY TO SEVERELY ACTIVE RA

- Patients with moderately to severely active RA are at greater risk of developing joint damage and disability than patients with mildly active disease . These patients typically meet the *American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria for RA* and exhibit a combination of the following:

1. At least **5 inflamed joints**
2. **Elevation in the ESR** and/or serum CRP concentration
3. **Positive RF** and/or anticyclic citrullinated peptide (CCP) antibodies
4. **Evidence of inflammation** on plain radiography of the hands, wrists, or feet, such as osteopenia and/or periarticular swelling. In addition, minimal joint space narrowing and small peripheral erosions may be observed.

Definition of resistance to initial DMARDs

Resistance to initial DMARD therapy is defined as one of the following:

- **Failure to achieve remission or low disease activity** within 3-6 mnths of initiating (MTX) or other DMARD therapy in maximally tolerated doses.
- A requirement, in addition to DMARDs, for **chronic glucocorticoid therapy** in a dose of greater than about 5-7.5 mg/day of **prednisone** or equivalent to achieve or maintain remission or low disease activity after 3-6 mnths of Rx with DMARDs.
- **A requirement for multiple courses with glucocorticoids**, in excess of doses used for chronic therapy, for the treatment of recurrent disease flares.

- **USE OF ANTIINFLAMMATORY THERAPY,INCLUDING NSAIDS & GLUCOCORTICOIDS TO HELP CONTROL THE SYMPTOMS & IMPROVE FUNCTION UNTIL DMARDS TAKE EFFECT.**

- **ACHEIVEMENT AND MAINTENANCE OF TGHT CONTROL OF DISEASE ACTIVITY , DEFINED AS REMISSION OR A STATE OF LOW DISEASE ACTIVITY.**

Early use of DMARDs

mildly active RA	Initiate antiinflammatory therapy with a NSAID for rapid symptomatic relief and begin DMARD treatment with either hydroxychloroquine (HCQ) or sulfasalazine (SSZ).
moderately to severely active RA,	Initiate antiinflammatory therapy with either a NSAID or glucocorticoid, and generally start DMARD therapy with methotrexate (MTX).
resistant to initial DMARD therapy (eg, MTX)	treat with a combination of DMARDs (eg, MTX plus either a TNF inhibitor or SSZ and HCQ) or, alternatively, we switch the patient to a different DMARD of potentially comparable efficacy (eg, leflunomide or a TNF inhibitor), while also treating the active inflammation with antiinflammatory drug therapy.

Rheumatoid arthritis

Mild

NSAIDs or hydrochloroquine

Moderate/severe

Non-biologic DMARDs
methotrexate, hydroxychloroquine, sulfasalazine
(combinations with MTX recommended)

TNF α-blockers
etanercept, adalimumab or infliximab

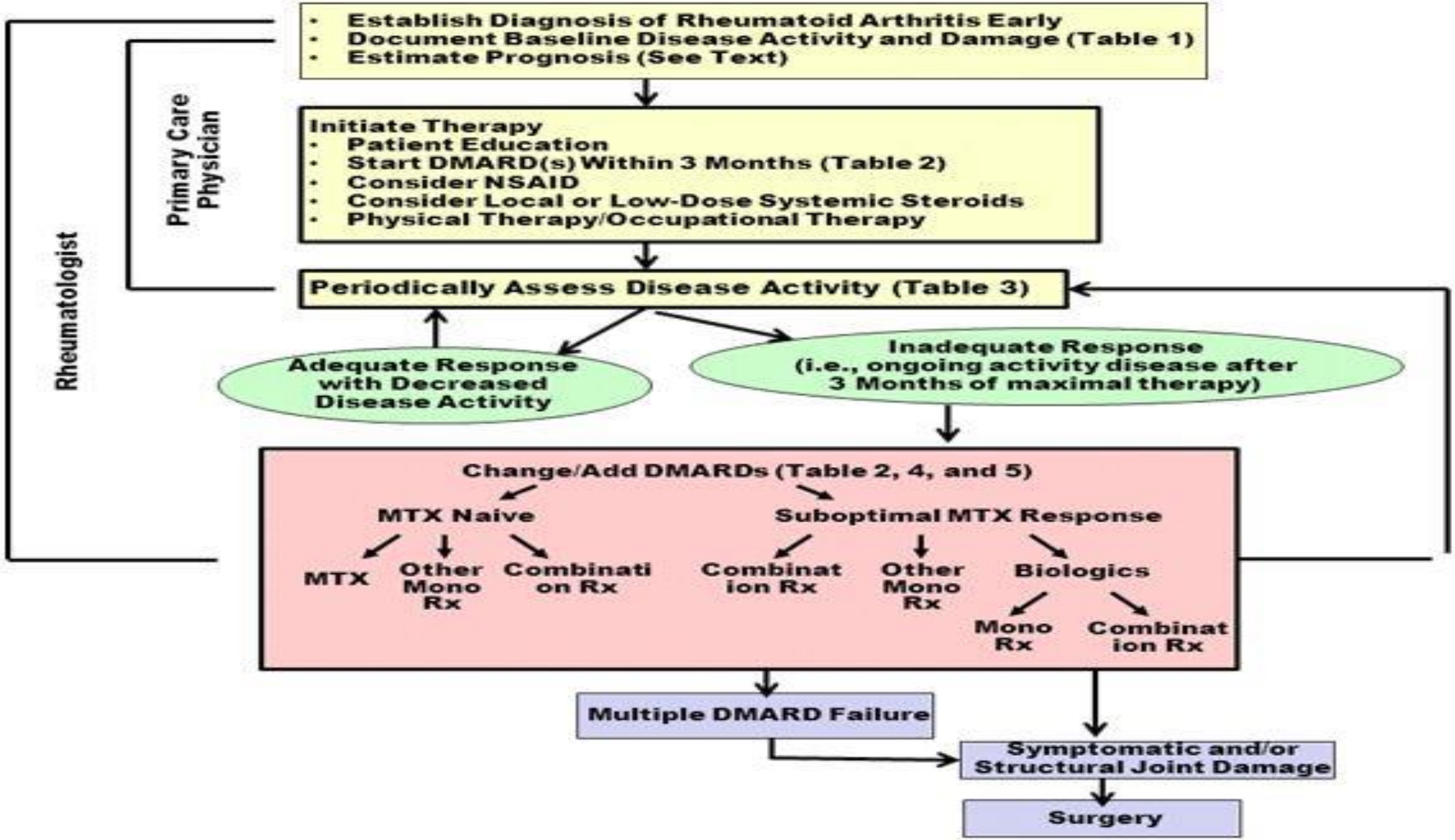
B-cell depleting therapy

2016 EULAR Recommendations -12

- Patients with active disease should be monitored every 3 months, and treatment should be adjusted if there is no improvement at 6 months
- Methotrexate (MTX) is recommended as first-line therapy; sulfasalazine (SSZ) or leflunomide can be substituted if there are contraindications to MTX
- Tumor necrosis factor (TNF) inhibitors are no longer the only biologics recommended for patients with an insufficient response to MTX; all biologics are considered to be similarly effective
- Biologics should be combined with disease-modifying antirheumatic drugs (DMARDs)

Disease Activity	Recommendations
Early RA (<6 months) **(Notable change from 2012 to 2015 guidelines: The 2015 guidelines do not recommend initial combination DMARD therapy in early RA with moderate to high disease activity)**	• Administer DMARD monotherapy in patient with low-high disease activity • If disease activity remains moderate /high despite DMARD monotherapy, use combination DMARDs or a TNF inhibitoror a non-TNF biologic
Established RA (=6 month or meets 1987 ACR RA classification criteria)	If disease activity remains moderate or high despite DMARD monotherapy, ACR guidelines recommend one of the following: • Combination DMARDs • Add an anti-TNF biologic • Non-TNF biologic • Tofacitinib
If disease activity remains moderate or high despite use of a single anti-TNF biologic:	• Switch to a non-TNF biologic with or without MTX over another anti-TNFi or Tofacitinib
If disease activity remains moderate or high despite use of one anti-TNF biologic and one non-TNF biologic:	• Use another non-TNF biologic with or without MTX over Tofacitinib • If still uncontrolled use Tofacitinib
(Notable change from 2012 to 2015 guidelines: Instead of switching from one anti-TNF biologic to another anti-TNF biologic because of continued activity, it is recommended to change first to a non-TNF biologic)	

2015 ACR Guideline for the Treatment of RA
Monotherapy: Methotrexate or leflunomide recommended for all patients regardless of disease duration or severity
Dual-DMARD combinations: Methotrexate and hydrcosychloroquine recommended for moderate-to-high disease activity; Methotrexate or leflunomide with longer disease duration.
Triple-DMARD combinations: Methotrexate,sulfasalazine and hydrcosychloroquine recommended for patients with poor prognostic features and moderate-to-high levels of disease activity.
Anti-TNF-alpha agents: Etanercept, infliximad, adalimumab plus methotrexate recommended for patients with early RA(symptoms <3 months) with high disease activity and no history of ever being treated with DMARD. TNF blockers are recommended fo a long disease duration and for those patients who failed to obtain a satisfactory response from methotrexate therapy.
Abatacept or rituximab recommended for patients with at least moderate disease activity and poor prognostic indicators following treatment with methotrexate or other DMARDs resulting in inadequate treatment response
ACR-American College of Rheumatology; DMARDs- Disease-modifying antirheumatic drugs; RA – rheumatoid arthiritis; TNF – Tumor necrosis factor -Poor prognosis features include high number of affected joints, pra--- of bonyerosioes, elevated theumatoid factor for C-reactive protein, anticycle


Rheumatologist
Primary Care Physician
• Establish Diagnosis of Rheumatoid Arthritis Early
• Document Baseline Disease Activity and Damage (Table 1)
• Estimate Prognosis (See Text)
Initiate Therapy
• Patient Education
• Start DMARD(s) Within 3 Months (Table 2)
• Consider NSAID
• Consider Local or Low-Dose Systemic Steroids
• Physical Therapy/Occupational Therapy
Periodically Assess Disease Activity (Table 3)
Adequate Response with Decreased Disease Activity
Inadequate Response (i.e., ongoing activity disease after 3 Months of maximal therapy)
Change/Add DMARDs (Table 2, 4, and 5)
MTX Naive
Suboptimal MTX Response
MTX
Other Mono Rx
Combination Rx
Combination Rx
Other Mono Rx
Biologics
Mono Rx
Combination Rx
Multiple DMARD Failure
Symptomatic and/or Structural Joint Damage
Surgery

PROGNOSIS

- **OUTCOME IN RA IS COMPROMISED WHEN DIAGNOSIS AND TREATMENT ARE DELAYED.**
- **OUTCOMES ARE HIGHLY VARIABLE.SOME PATIENTS EXPERIENCE A RELATIVELY SELF LIMITING DISEASE WHILE OTHERS HAVE A CHRONIC PROGRESSIVE ILLNESS.**
- **40% OF THE PATIENTS BECOME DISABLED AFTER 10 YEARS.**
- **INTERVENTIONS WITH DMARDS IN VERY EARLY RA(SYMPTOM DURATION OF LESS THAN 12 WEEKS AT THE TIME OF FIRST TREATMENT) GIVES THE BEST OPPURTUNITY FOR ATTEMPTING TO ACHIEVE DISEASE REMISSION.**

UNFAVOURABLE PROGNOSTIC FACTORS

- **HLA DR4 GENOTYPE**
- **HIGH SERUM TITER OF AUTOANTIBODIES(RF & ACPA)**
- **PRESENCE OF EXTRAARTICULAR MANIFESTATIONS**
- **LARGE NUMBER OF INVOLVED JOINTS**
- **AGE YOUNGER THAN 30 YEARS**
- **FEMALE SEX**
- **PRESENCE OF SYSTEMIC SYMPTOMS**

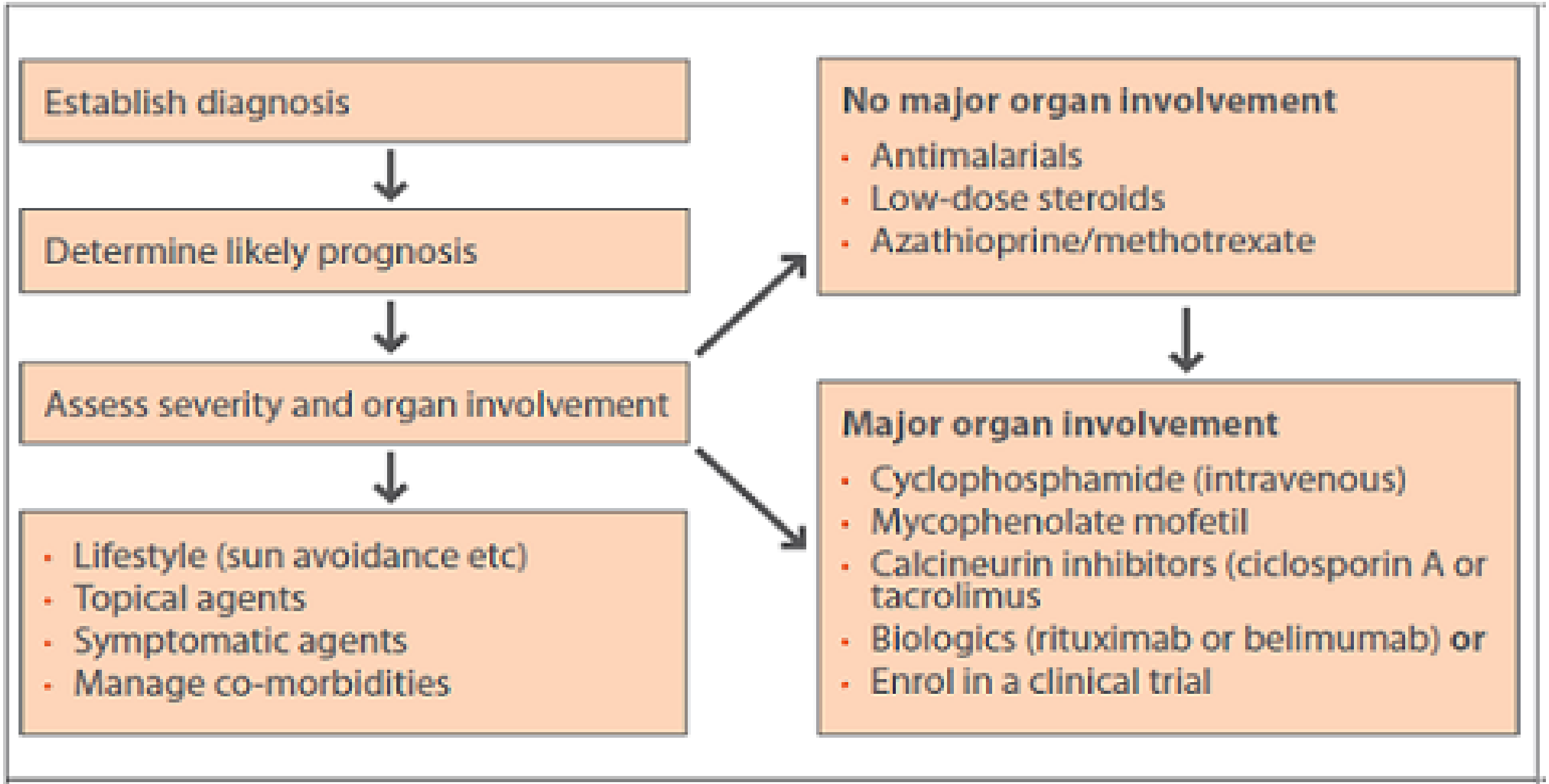
SYSTEMIC LUPUS ERYTHEMATOSUS

- MANAGEMENT DEPENDS ON DISEASE SEVERITY AND DISEASE MANIFESTATIONS.
- HYDROXYCHLOROQUINE HAS A CENTRAL ROLE FOR LONG TERM TREATMENT IN ALL PATIENTS.

  DECREASES NUMBER OF FLARES AND PROLONGS LIFE

  CORNERSTONE OF SLE MANAGEMENT

- **SLE WITH ARTHRITIS – NSAIDS, HCC, short courses of STEROIDS.**



Overview of the management of systemic lupus erythematosus.

AOSD

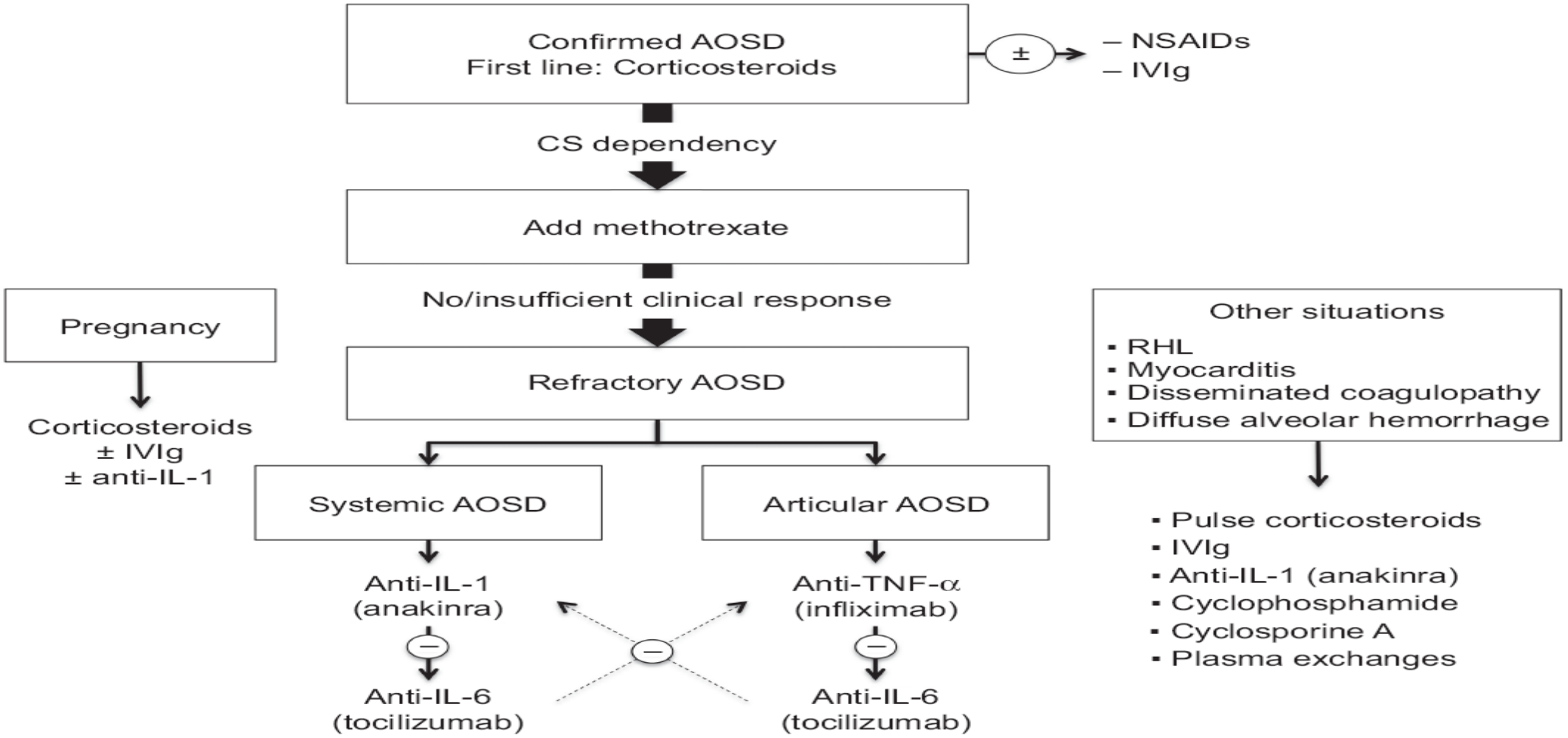
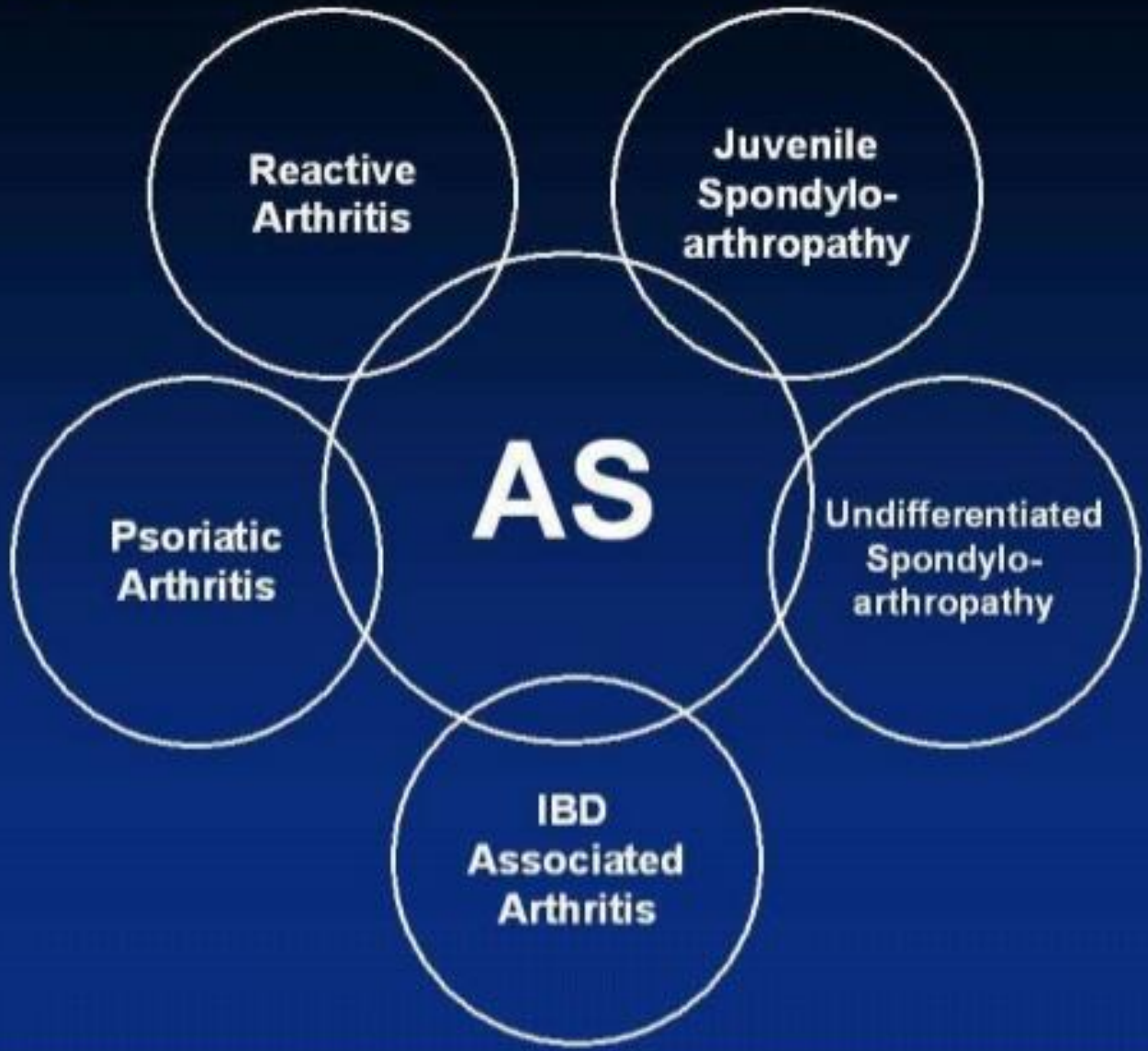


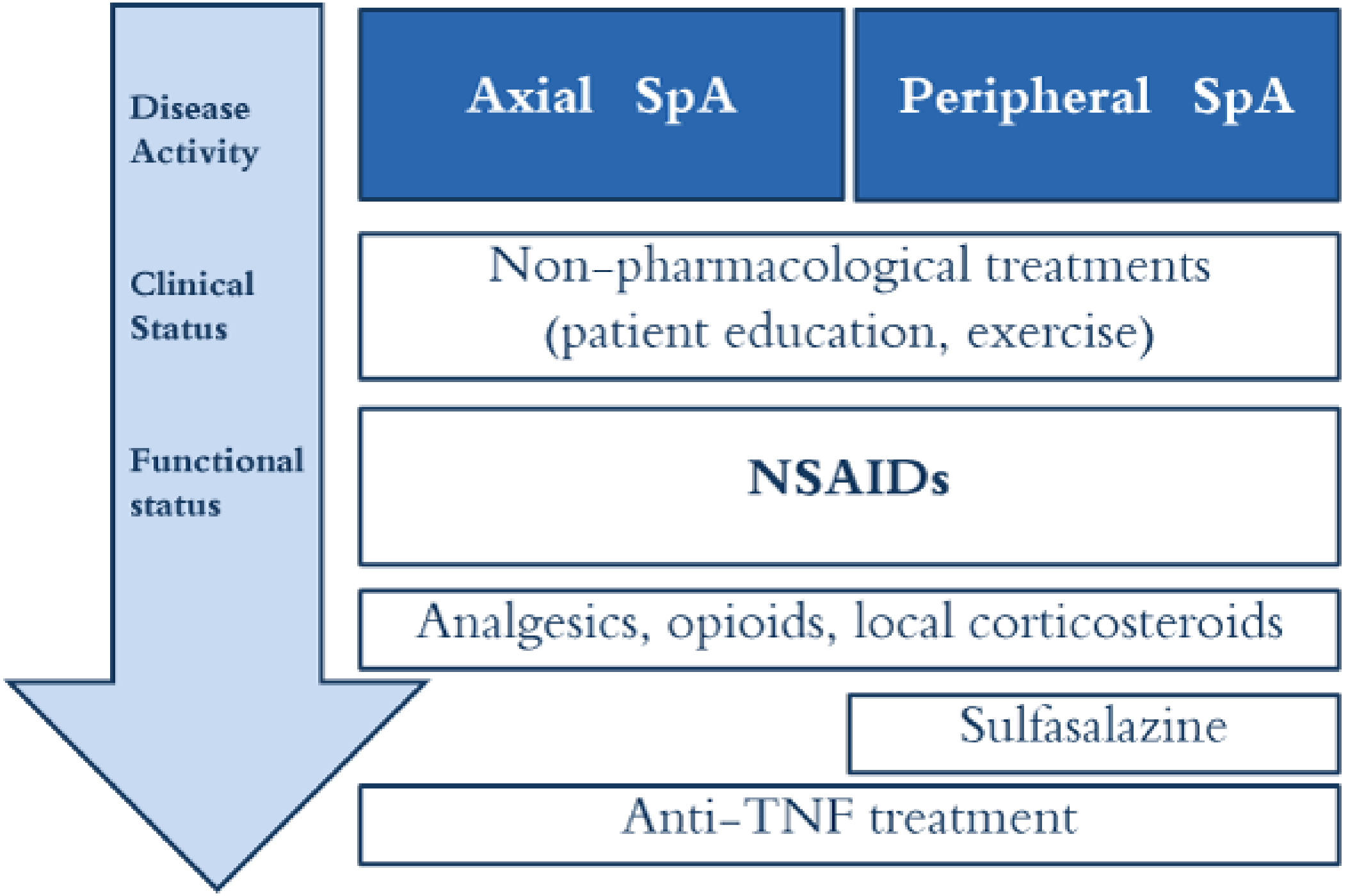
Figure 1 Management algorithm for adult-onset Still's disease.
Abbreviations: AOSD, adult-onset Still's disease; CS, corticosteroids; IVIg, intravenous immunoglobulin; NSAIDS, nonsteroidal anti-inflammatory drugs; RHL, reactive hemophagocytic lymphohistiocytosis.

Family of Spondyloarthropathies



Seronegative Spondyloarthropathies

- Seronegative (test negative for RF)
- Presence of HLA B27 (Class I)
- Inflammation of the sacroiliac joint and spine
- Enthesitis: Inflammation at insertion sites of tendon or ligament to bone
- Asymmetric Inflammatory Arthritis
- Extrarticular Disease


Disease Activity
Clinical Status
Functional status
Axial SpA
Peripheral SpA
Non-pharmacological treatments (patient education, exercise)
NSAIDs
Analgesics, opioids, local corticosteroids
Sulfasalazine
Anti-TNF treatment

Gout
Treatment Options

Acute Gout

- NSIADs
- Colchicine
- Steroids

Prevention of Recurrent Attacks

Modify risk factors

Obesity, Die, Alcohol, Diuretics, HTN

Uricosuric Agents

Probenecid, Sulfinpyrazole

Xanthine oxidase inhibitors

(can precipitate acute attacks so needs prophylaxis with NSAIDs/Colchicine/ Steroids)

Allopurinol Febuxostat

Renal Failure must prompt caution with NSAIDs, Colchicine, Probenecid, Sulfinpyrazole and Allopurinol

Pseudogout

- Treatment
  - Avoid joint overuse
  - NSAIDs
  - Colchicine, though less effective than in acute gout
  - Synovial fluid aspiration
  - Intra-articular steroids
  - No proved effective agents to dissolve CPPD crystals
  - Joint replacement in destructive disease, with symptoms resistant to drugs

THANK YOU