



**2021 ACOI Annual Convention
And Scientific Sessions
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Rheumatology Reactive Arthritis What You Need To Know

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Disclosures

No Current Disclosures

Previous Clinical Research:

Daichi-Sankyo

GSK

Bristol Myers Squibb

Wyeth

Rigel

Genentech/Roche

Jazz Pharmaceuticals

Novartis

Centocor

Learning Objectives



Review Normal Immunity and Autoimmunity

Review Spondyloarthropathy

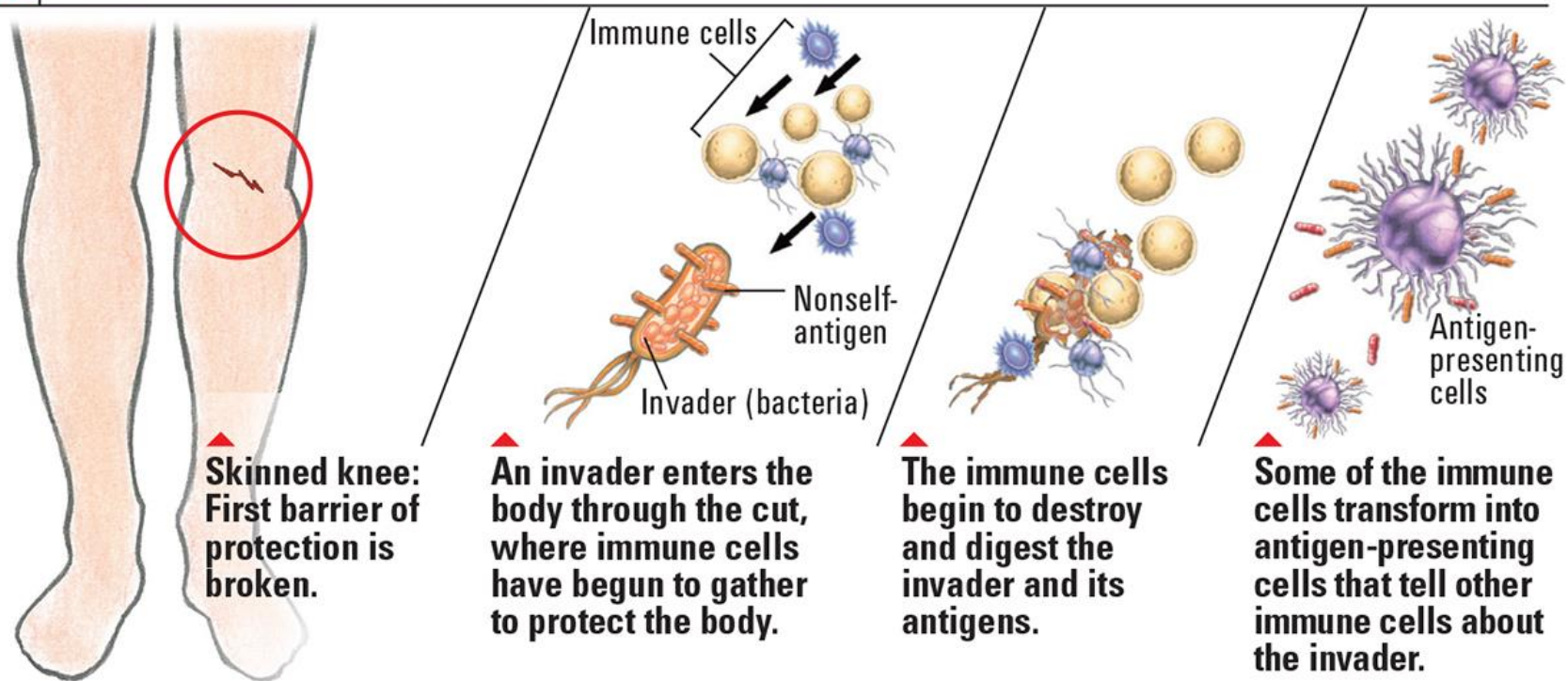
Discuss Reactive Arthritis and its features

Discuss implicated infections, viruses, coronavirus

Disease course and treatment options

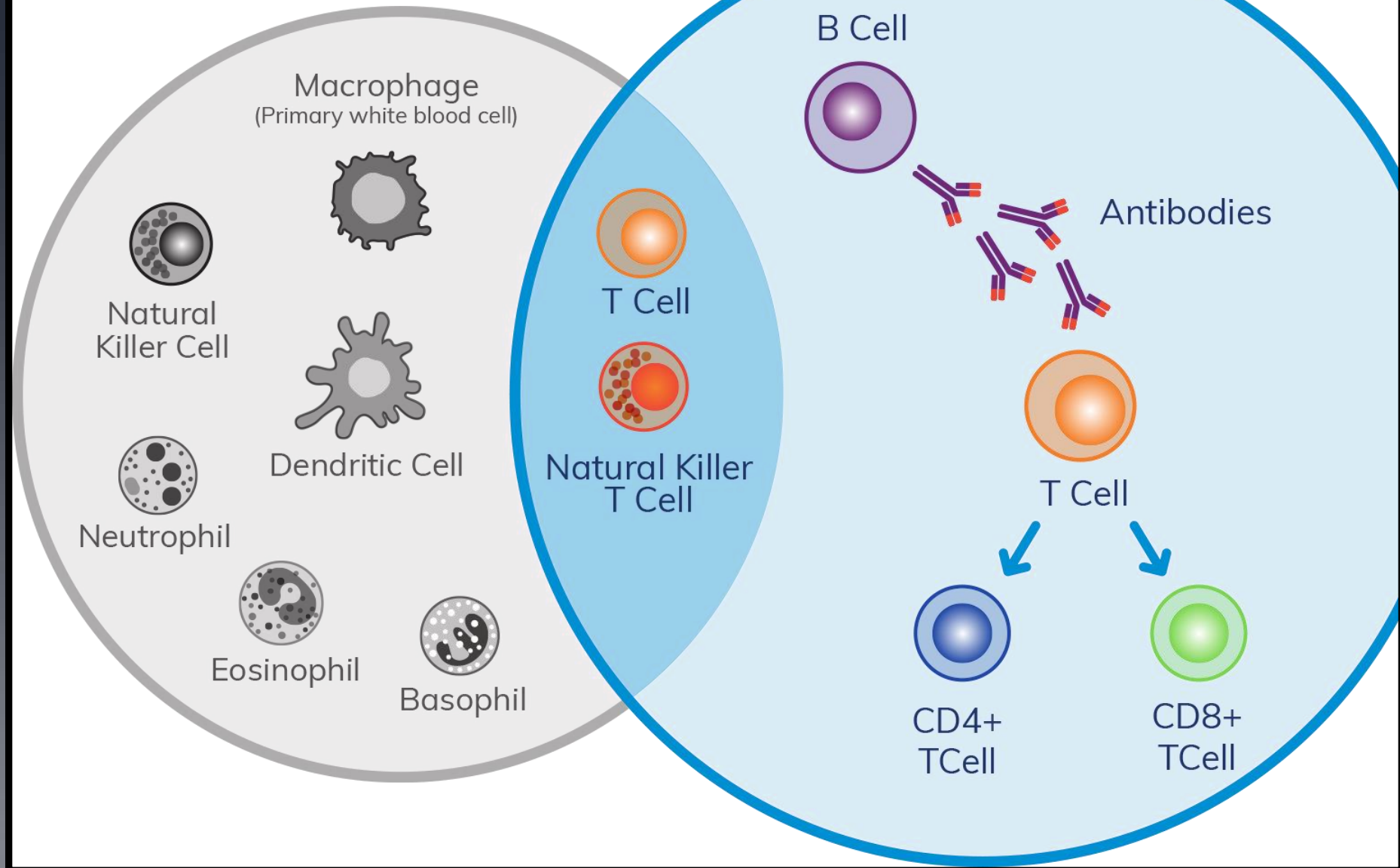
Normal Immunity

FIGURE 2
NORMAL IMMUNE RESPONSE



ADAPTIVE Immunity

INNATE Immunity



AUTOIMMUNE DISEASES

Brain
Multiple Sclerosis
Guillain-Barre Syndrome
Autism



Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease



Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia



Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

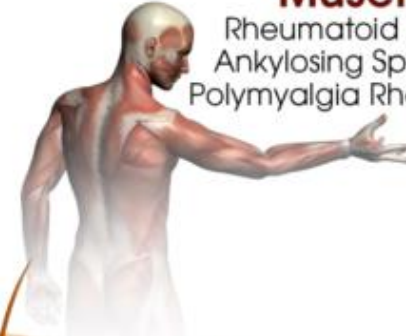


GI Tract
Celiac's Disease
Crohn's Disease
Ulcerative Colitis
Diabetes Type I



**Over 100
Different Types of
Autoimmune
Disorders**

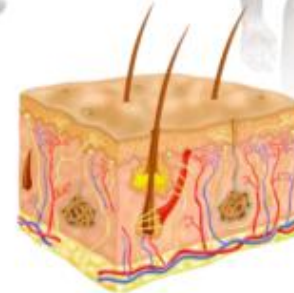
Muscles
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica



Nerves
Peripheral Neuropathy
Diabetic Neuropathy



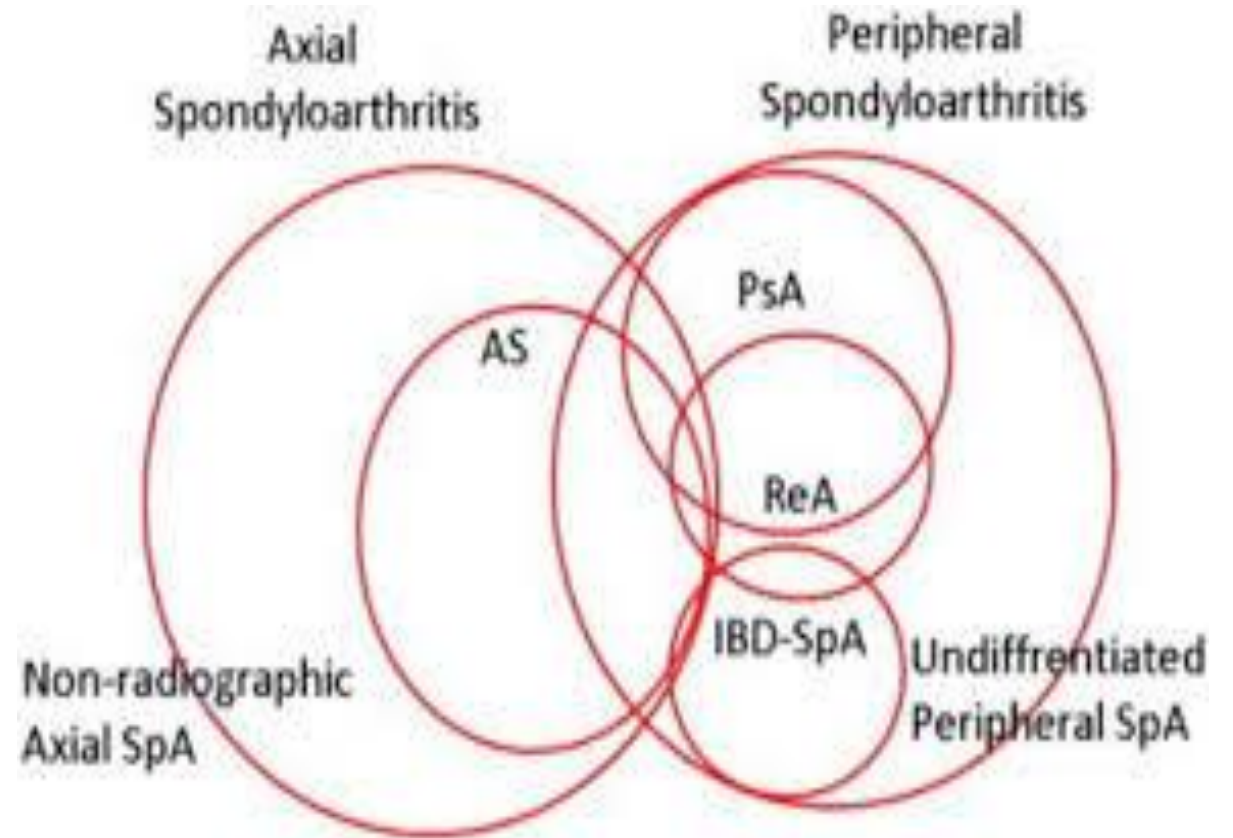
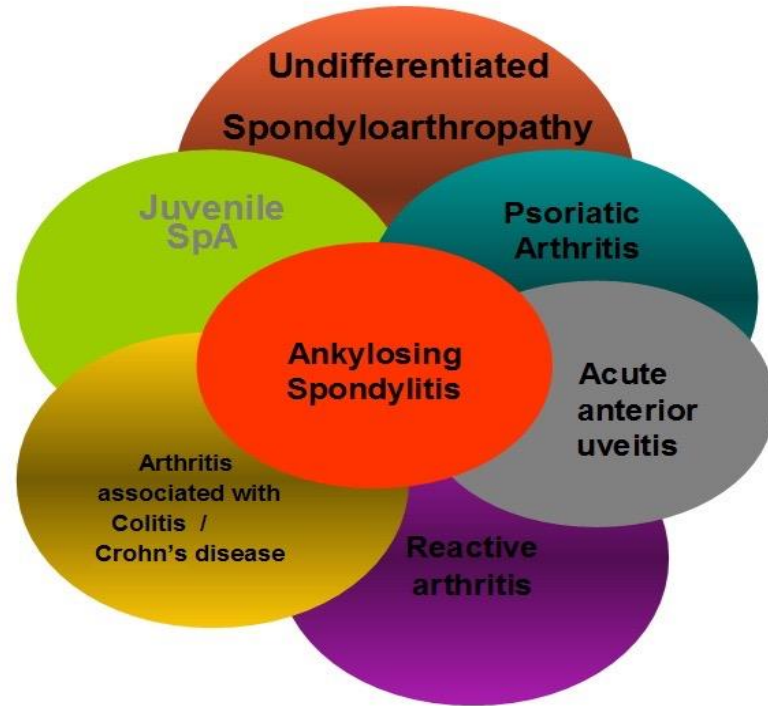
Skin
Psoriasis
Vitiligo
Eczema
Scleroderma



Lung
Fibromyalgia
Wegener's Granulomatosis

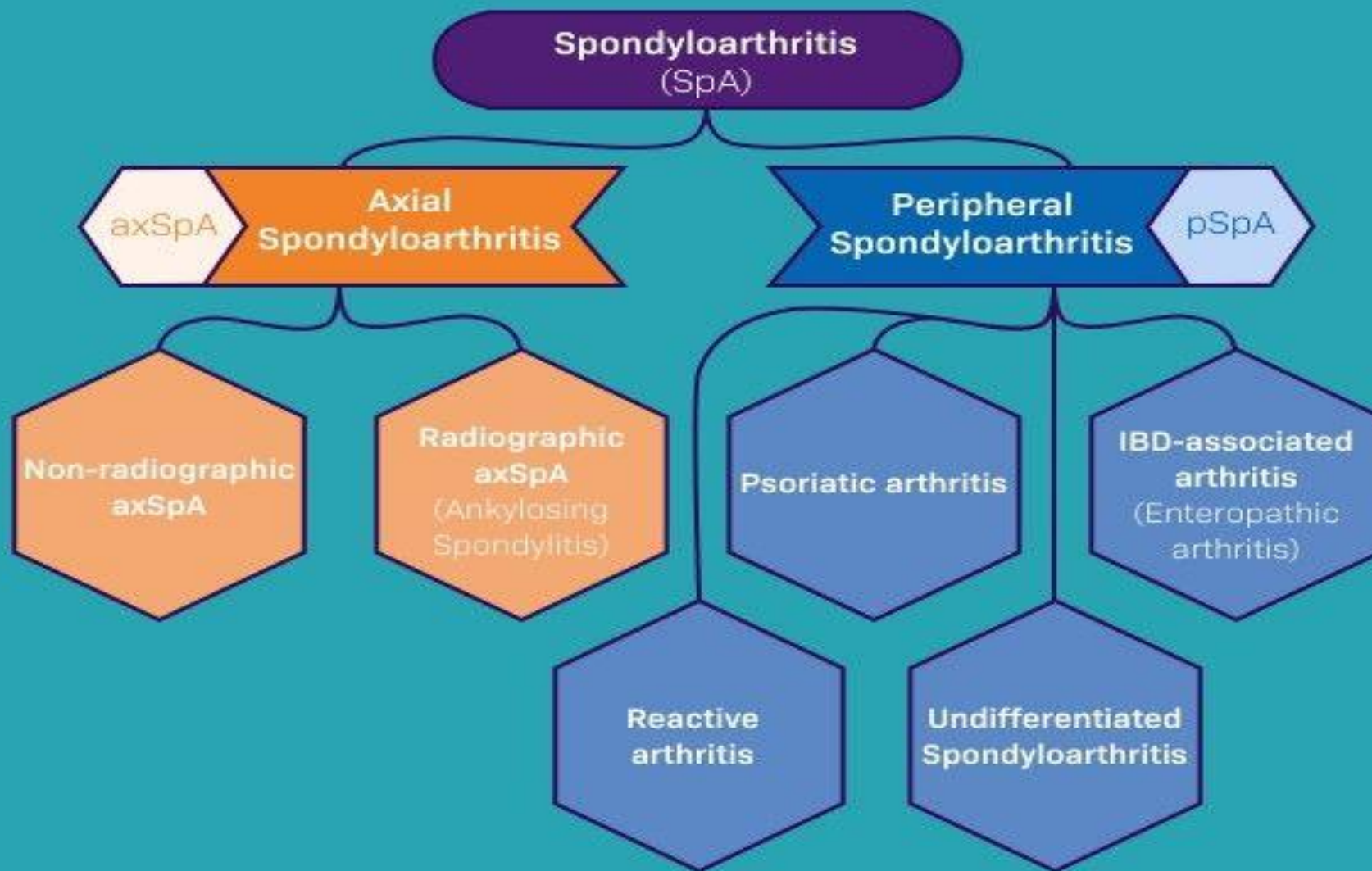


Spondyloarthropathy (SpA)



- Seronegative refers to a negative RF
- Spondylitis - radiographically or not - is a linking feature

Types of Spondyloarthritis



Spondyloarthritis Subtypes



Spondyloarthritis – main clinical manifestations

1. Axial involvement/spinal inflammation
2. Peripheral arthritis
3. Peripheral enthesitis

Reactive Arthritis

- Triggered by an infection most often in the intestines, genitals or urinary tract
 - Joint pain and swelling usually targets the lower back, buttocks, knees, ankles, heels and feet
 - Low back pain tends to be worse at night or in the morning
 - Inflammation also can affect the eyes, skin, urethra, prostate gland and cervix
 - Skin changes can also occur and include a rash on the soles and palms as well as mouth sores
-

Reactive Arthritis

- Formerly known as Reiter's Syndrome, named after the Nazi war criminal Hans Reiter's description of the condition in 1916
 - Fiessinger-Leroy disease is a synonym, named after Reiter's patient
 - Autoimmune condition that develops in response to an infection usually after 3-4 weeks
 - Syndrome is usually short lived in most patients lasting 3-12 months
 - Approximately 30% patients will go onto develop a long-term inflammatory arthritis however such as PsA, SpA, AS or RA
-

Organisms Associated with ReA

C trachomatis/ C pneumoniae, [28] including *C trachomatis* serovars L2 in lymphogranuloma venereum [29, 30]

Ureaplasma urealyticum

Neisseria gonorrhoeae

Shigella flexneri

Salmonella enterica serovars Typhimurium, Enteritidis, [31] and Hadar [32]

Mycoplasma pneumoniae

Mycobacterium tuberculosis [33]

Cyclospora [34]

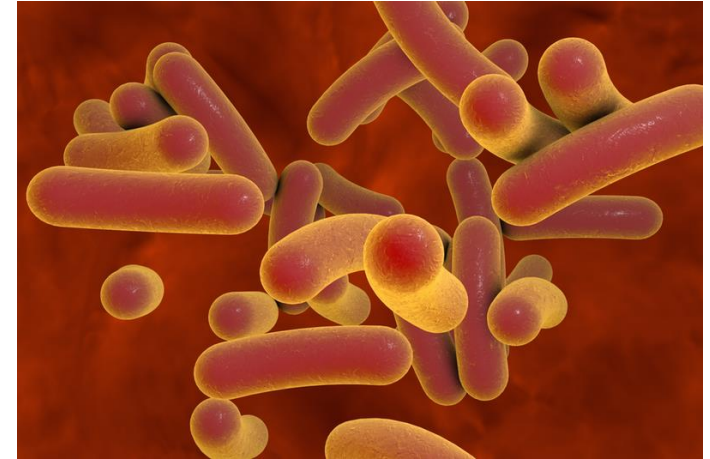
Yersinia enterocolitica and *Y pseudotuberculosis*

Campylobacter jejuni [35] and *C coli*

Clostridium difficile

Beta-hemolytic [21] (eg, group A [36]) and viridans streptococci

Coronaviruses including SARS-CoV-2



Cheeti A, Chakraborty RK, Ramphul K. Reactive Arthritis. 2020 Jan. [\[Medline\]](#). [\[Full Text\]](#).

Classic Triad / Tetrad of ReA

- Arthritis and Enthesitis – usually Monoarticular or
- Asymmetrical Oligoarticular in weight bearing joints
- Conjunctivitis – erythema, burning, photophobia
- Noninfectious urethritis – dysuria, urgency
- Mucocutaneous findings
- Found in only 1/3 of patients

Wu IB, Schwartz RA. Reiter's syndrome: the classic triad and more. *J Am Acad Dermatol*. 2008 Jul. 59(1):113-21. [\[Medline\]](#)

ReA Physical Findings - Musculoskeletal

- Enthesopathy, enthesitis, inflammation at tendon or ligament insertions into bone - attachment of the Achilles tendon and the plantar fascia to the calcaneus
- Dactylitis with sausage digits





ReA Physical Findings - Musculoskeletal

Asymmetric oligoarthritis
Affects weight-bearing joints
Predominantly lower extremities
Sacroiliitis



ReA Physical Findings—
Skin and Nails

Keratoderma blennorrhagicum
Erythema nodosum
(uncommon)
Onychodystrophy

Physical Findings in ReA – Skin and Nails

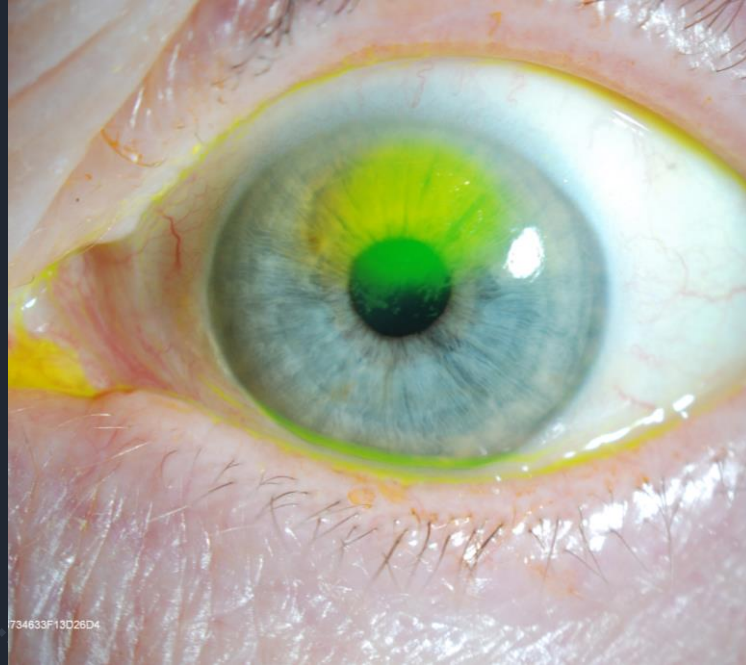
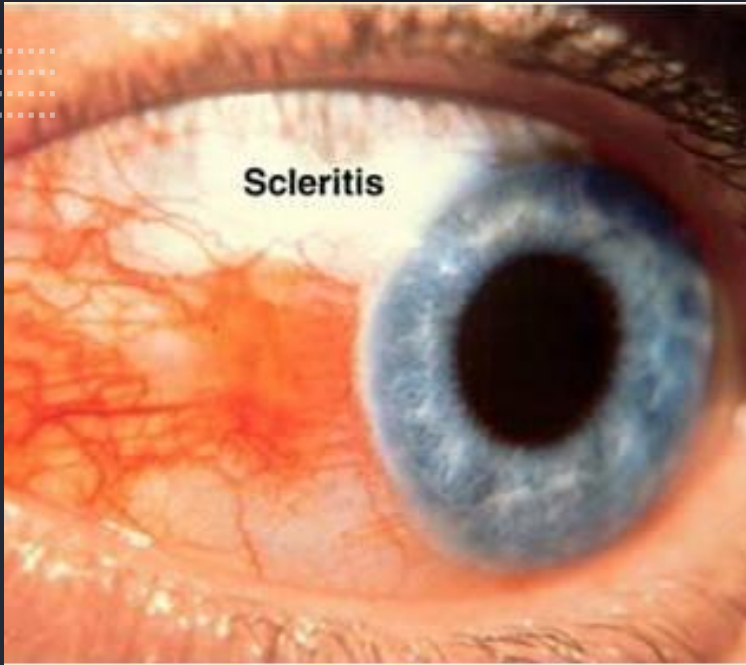
Psoriasis
Psoriaform
Guttate
Pustular
Inverse
Eczematous



ACO*i*



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ReA Physical Findings— Eyes

Conjunctivitis, anterior uveitis
Keratitis, scleritis, episcleritis
Hypotony, glaucoma, corneal
ulceration
Retinal edema, retinal vasculitis,
Dacryoadenitis, iridocyclitis



ReA Physical Findings— GU Tract

- Meatal edema and erythema
- Clear mucoid discharge, prostatitis
- Vulvovaginitis, circinate balanitis
- Cervicitis, cystitis, salpingo-oophoritis
- Pyelonephritis, bartholinitis

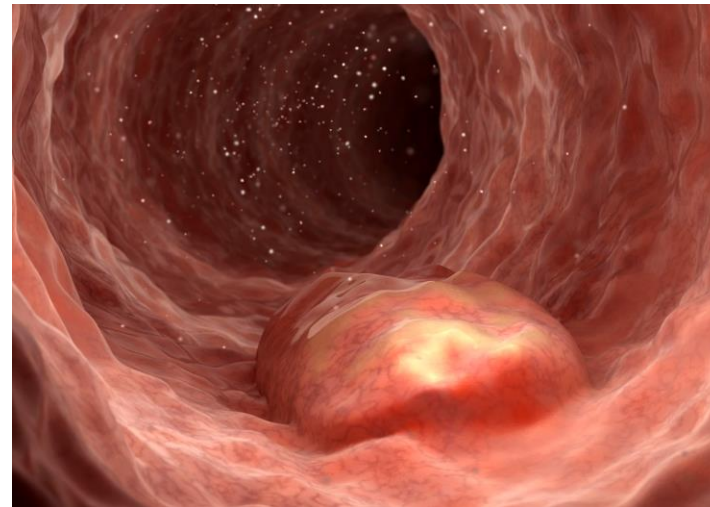


Editorial Wolters Kluwer; 2007; Capitulo 18; Pagina: 548.
14ª Edición; Editorial Ciencias Médicas; 2004.

ReA Physical Findings –GI Tract



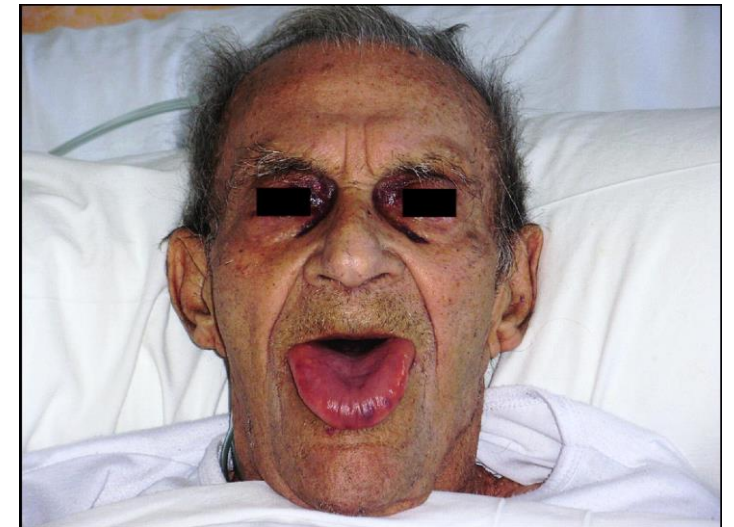
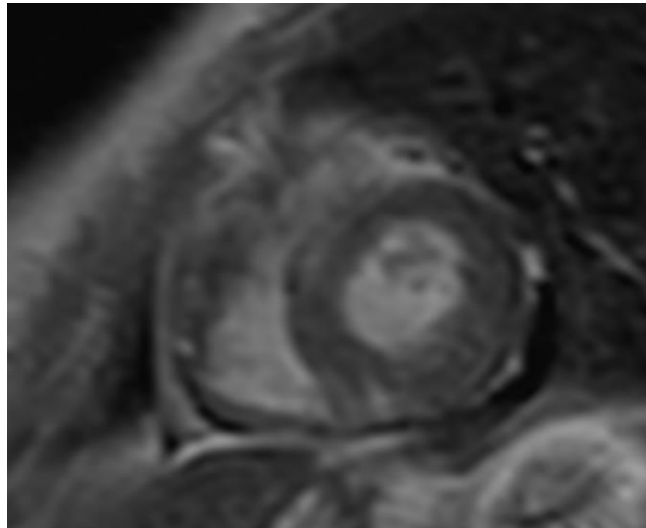
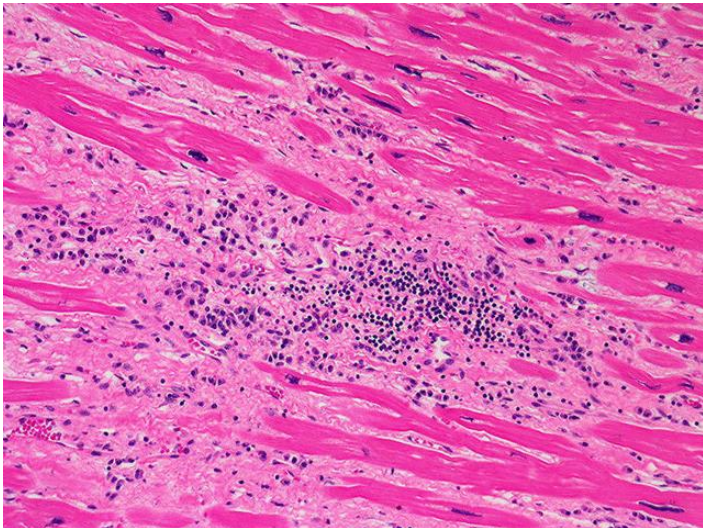
- Diarrhea; abdominal pain; lesions resembling inflammatory bowel disease on ileocolonoscopy



ReA Physical Findings– Other Systems



- Cardiac -aortitis, aortic regurgitation, transient conduction abnormalities, myocarditis, pericarditis
- Renal -proteinuria, microhematuria, amyloid deposits, immunoglobulin A [IgA] nephropathy



ReA Diagnosis- Labs

- Clinical: based on H&P and exam
 - White blood cell (WBC) and red blood cell (RBC) counts
 - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and other acute-phase reactants
 - IgA antibodies to specific bacterial antigens
 - Serology and cultures (blood, urine, stool, cervix, urethra), particularly for *Chlamydia*
 - Human leukocyte antigen (HLA)–B27
 - Tuberculin skin test, HIV, Urinalysis
 - Antistreptolysin O (ASO) or anti-DNase B testing (if poststreptococcal infection is suspected)
-

ReA Diagnosis - Studies

- Helpful Imaging and studies:
 - Plain radiography (reveals findings in only 40-70% of cases)
 - Magnetic resonance imaging (MRI) and Ultrasound (US)
 - Computed tomography (CT)
 - Echocardiography and EKG
 - Whole-body scintigraphy and Positron emission tomography (PET)
 - Arthrocentesis, synovial fluid analysis
-

ReA – Risk Factors

- **Age.** Mostly adults between the ages of 20 and 40.
- **Sex.** Women and men are equally likely to develop reactive arthritis in response to foodborne infections. Men are more likely than to develop reactive arthritis in response to sexually transmitted bacteria.
- **Hereditary factors.** HLA-B27, as well as those with a strong family clustering of the disease, tend to develop more severe and long-term disease

Amor B, Santos RS, Nahal R, Listrat V, Dougados M. Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol.* 1994 Oct. 21(10):1883-7. [\[Medline\]](#)

ReA –Mechanism of Action

- Microbial antigens cross-react with self-proteins, stimulating and perpetuating an autoimmune response mediated by type 2 T helper (Th2) cells.
 - Chronicity and joint damage have been associated with a Th2 cytokine profile that leads to decreased bacterial clearance
 - Proinflammatory cytokines. Native T cells under the influence of transforming growth factor (TGF)- β and other cytokines, such as interleukin (IL)-6, differentiate into Th17 effector cells, which then produce IL-17 which are elevated in synovial fluid
 - Deficiencies in regulatory mechanisms result in increased proinflammatory cytokine production and
-

ReA Therapies

Actions and Effects

NSAID and COX-2 inhibitors

- Reduces joint pain and inflammation
- No effect on progression of disease
- GI and CV side effects

Oral steroids

- Relieve pain and inflammation
- May slow disease progression, work quickly
- May work as a bridge therapy until others reach efficacy
- Long-term use associated with many side effects including osteoporosis, skin fragility, diabetes, Cushing's disease, atherosclerosis

DMARDs (Disease Modifying Antirheumatic Drugs)

- May slow progression of disease
- May take 4–24 weeks to obtain clinical benefit
- Side effects variable and based on DMARD prescribed
- Methotrexate, leflunamide, hydroxychloroquine, azathioprine, sulfasalazine, cellcept, cyclosporine

ReA Therapies

- Treatment may require the coordinated efforts of a team of specialists. Orthopedists, ophthalmologists, dermatologists, urologists, gynecologists and other health care professionals may need to systematically and comprehensively plan appropriate therapy
 - Physical therapy and exercise can be beneficial in promoting and improving joint function. Strengthening and range-of-motion exercises can be used to help preserve or improve joint function.
 - Studies into the benefit of prolonged antibiotic therapy for individuals with reactive arthritis have been inconsistent and inconclusive.
-

Poststreptococcal Reactive Arthritis (PSRA)

- Association with streptococcal infection – usually tonsillitis or pharyngitis
- Usual is group A streptococcus, although can occur with groups B, C or G
- Males and females are affected equally, both as adults and children
- Age distribution is bimodal, with a peak at ages 8–14 and another at age 21–37
- Subset of patients are HLA-B27-positive and are more likely to develop sacroiliitis. Association with HLA DRB*01 can also be seen
- Value of antibiotic treatment during the acute infection unknown

Poststreptococcal reactive arthritis: what is it and how do we know? S. L. Mackie, A. Keat

Rheumatology, Volume 43, Issue 8, August 2004, Pages 949-954, <https://doi.org/10.1093/rheumatology/keh225>

Rheumatic Fever

Rare in the US – occurring mostly in undeveloped nations

Inflammatory disease after strep throat or scarlet fever that is not treated

Mostly affects children between ages 5-15 although it can be in adults

Symptoms can include fever, painful / tender / swollen joints, small painless bumps under the skin, fatigue, Sydenham chorea (jerky uncontrolled movements hands, feet, face, crying, laughing), chest pain, murmur (can permanently damage the heart and valves)

Certain streptococcal bacteria have a protein similar to body tissues that tricks the body into attacking itself through an immune reaction causing inflammation in tissues

Chikungunya Virus ReA

Chikungunya virus is commonly associated with postviral arthralgia in 50% of patients

A similar phenomenon of postviral inflammatory arthritis was reported by Ghauri et al. after a Chikungunya virus epidemic broke out in Pakistan in 2017.

A large cross-sectional study carried out by Dr. Chang on patients with chikungunya who developed inflammatory arthritis, but the synovial fluid did not reveal the presence of the virus.

Based on this, the arthritis is thought to be secondary to the induction of host autoimmunity

Lyme Disease leading to ReA, SpA, RA

Most common vector-borne disease in the US transmitted through ticks

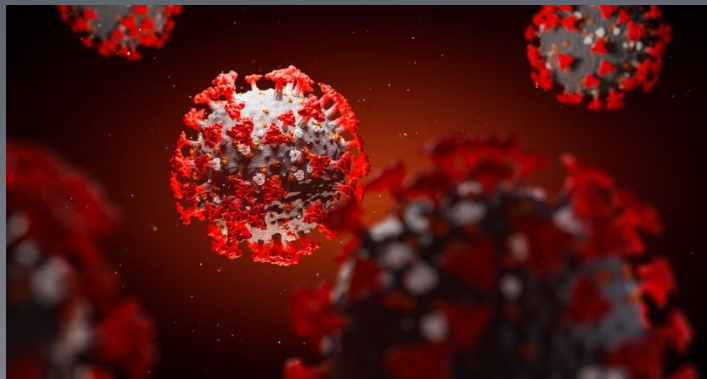
- Caused by bacterium *Borrelia burgdorferi*, rarely *Borrelia mayonii*
- Typical symptoms include headache, fever, fatigue, rash (erythema migrans) and if left untreated can spread to joints, heart and nervous system
- Diagnosis is based on symptoms, physical exam and exposure of the tick
- CDC recommends 2 step testing process using EIA enzyme immunoassay or immunofluorescence assay followed by Western immunoblot for positives
- Treatment is a 4 week course antibiotics, perhaps a second
- Arthritis after antibiotics is considered immune mediated



Coronavirus and Reactive Arthritis

- Respiratory viral infections may put patients at risk for developing Re A and [rheumatoid arthritis](#) (RA), according to a report published in [Arthritis Research & Therapy](#), suggesting concerns for patients who develop coronavirus.

Joko, Y.B., Lim, YH., Kim, KJ. *et al.* Respiratory viral infections and the risk of rheumatoid arthritis. *Arthritis Res Ther* **21**, 199 (2019).
<https://doi.org/10.1186/s13075-019-1977-9>

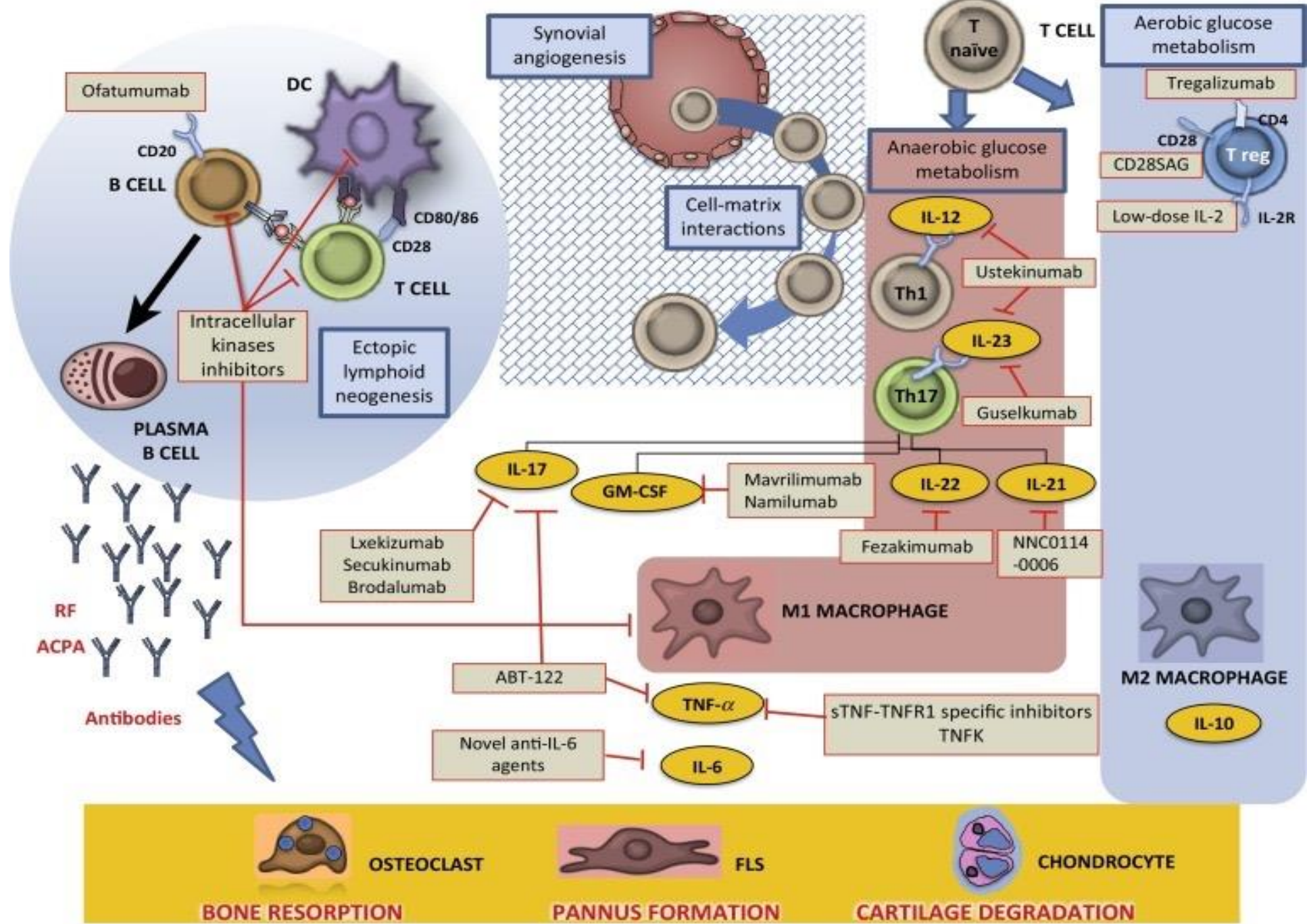


- The study authors queried the Korean National Health Insurance (KNHI) claims database for records spanning 2011 through 2015; data collection included patients' diagnoses, procedures, prescriptions, type of institution or department, and individual beneficiary information. The Korea Centers for Disease Control and Prevention database was queried for weekly observation data on coronavirus, as well as seven other respiratory viral infections: influenza, parainfluenza, adenovirus, respiratory syncytial virus (RSV), rhinovirus, metapneumovirus, and bocavirus.

ReA following COVID-19

- Most people who had coronavirus (COVID-19) recover completely in a few weeks
- Some continue to experience symptoms weeks and months after however
- This is known as post covid syndrome, "long haulers" or "long COVID-19"
- These health issues are sometimes called post-COVID-19 conditions and an inflammatory syndrome or arthritis is one of them

Carfi A, et al. Persistent symptoms in patients after acute COVID-19. JAMA. 2020; doi:10.1001/jama.2020.12603.

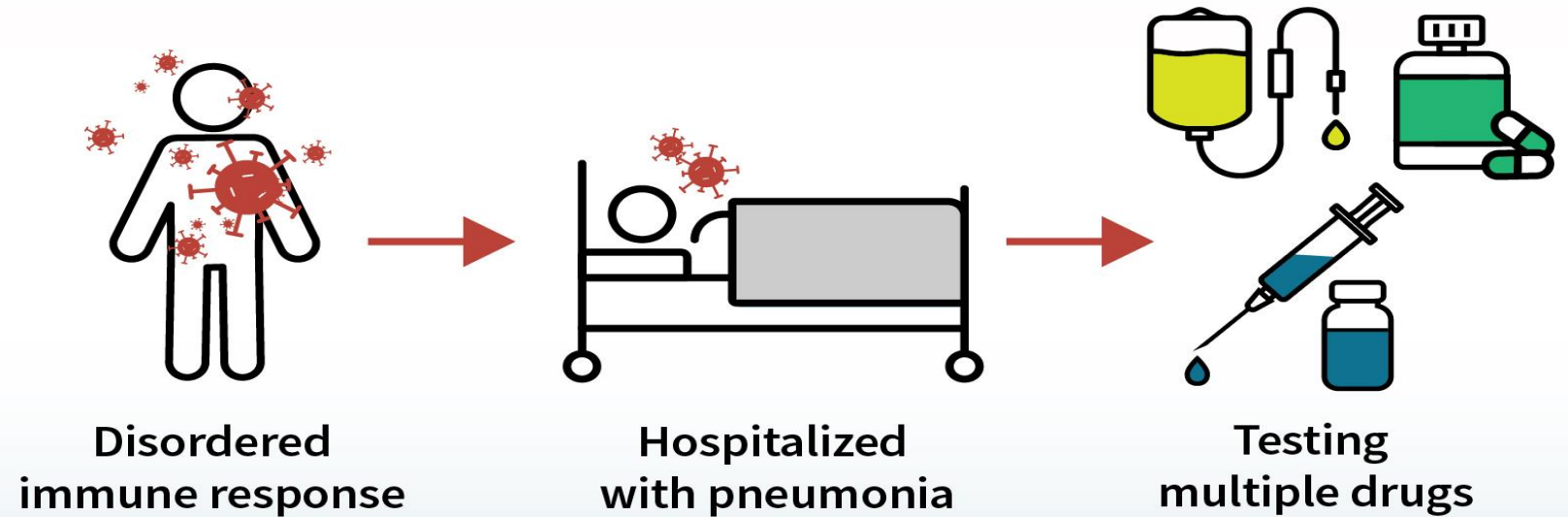


Cytokine Storm

- Cytokines are small proteins that send out signals that allow different immune cells to talk to each other and tell each other what to do.
 - Pro-inflammatory cytokines call upon the soldiers of the immune system (natural killer cells and CD8⁺ T cells) to combat an invader. Tumor necrosis factor (TNF) and interleukin-6 (IL-6) are examples- hence why they TNF-inhibiting medications (such as etanercept, adalimumab, and infliximab) or IL-6 blockers are used for autoimmune patients. Anti-inflammatory cytokines, such as IL-4 and IL-10, are released when the body is almost done fighting an invader to tell the immune system to back down.
 - When everything is working, pro-inflammatory cytokines and anti-inflammatory cytokines work together to kill off an invader then settle out of attack mode. When the immune system stays on the attack - a cytokine storm is the result.
-

Calming the storm

When the immune system overreacts to COVID-19, can immune modulator drugs change the outcome?



To learn whether a therapy will:

Tame immune response

Shorten hospital stay

Reduce need for ventilator

Emergency Use Authorization (EUA)

- November 19, 2020 - U.S. Food and Drug Administration (FDA) granted emergency use authorization (EUA) to baricitinib (Olumiant), oral Jak Inhibitor, combination with remdesivir (Veklury), for the treatment of seriously ill COVID-19 patients- hospitalized adults and children age 2 or older who require supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation.
- August 2, 2021 - FDA revised its Emergency Use Authorization (EUA) for Eli Lilly's and Incyte's COVID-19 treatment Olumiant (baricitinib) to authorize giving the drug alone



<https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/>

Emergency Use Authorization (EUA)

- June 24, 2021 Tocilizumab (Actemra) iv was authorized under section 564 FD&C Act for emergency use for hospitalized covid patients (2 years and older) who are receiving systemic steroids, require supplemental oxygen, non-invasive or invasive mechanical ventilation or ECMO.
- 4 trials RECOVERY 4116 hosp patients, EMPACTS 389 hosp patients, COVACTA 453 hosp patients and REMDACTA 649 patients. Three additional trials are currently enrolled.
- Dose of Tocilizumab is 4-8 mg/kg up to 800mg administered as a 60- minute intravenous infusion with dexamethasone (6mg daily for up to 10 days).



<https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/>

Vaccine considerations

ACR COVID-19 Vaccine Clinical Guidance Task Force

ACR guidelines indicate that all Rheumatic Patients be encouraged to get either mRNA vaccine series.

Theoretical risk exists for AIIRD flare or disease worsening following COVID-19 vaccination. However, the benefit of COVID-19 vaccination for RMD patients outweighs the potential risk.

Effects for 1-3 days can be: injection site pain, swelling at the site, fever, chills, fatigue and headache. Chest pain and shortness of breath are NOT expected. Flares can occur and if last longer than 72 hours can then be treated.

[LB0002 COVID-19 VACCINE SAFETY IN PATIENTS WITH RHEUMATIC AND MUSCULOSKELETAL DISEASE](#) P. M. Machado et al., Ann Rheum Dis, 2021



Thank You

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