ARTRITIS REACTIVA

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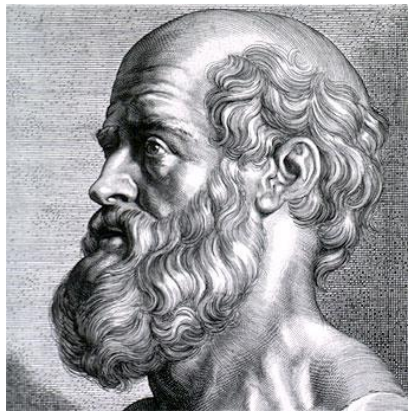
Historia



Hipócrates
Siglo IV a.C.

Enlaza "artritis" con "coito"

Cristobal Colón 1494

Primer caso conocido

Reiter-Fiessinger - Leroy 1916

5 Pacientes

García-Kutzbach, A., Chacón-Súchite, J., (2018). Reactive arthritis: update 2018. *Clinical rheumatology*, 1-6.

Generalidades

- Categorizada como una Espondiloartropatía inflamatoria*
- Se expresa como un síndrome inflamatorio agudo con afectación principal articular, que generalmente autorresuelve *
- Se piensa que ocurre en pacientes genéticamente predispuestos
- Inicia entre 1-4 semanas después de ciertas infecciones del TGU o TGI*
- Tradicionalmente se caracterizaba por la Triada Clásica -30%*

Schmitt, S. K. (2017). Reactive arthritis. *Infectious Disease Clinics*, *31*(2), 265-277.

Epidemiología*

Incidencia promedio de 1 a 30 casos por cada 100.000 hab

Aumenta la incidencia en el contexto de brotes de infección

Es más común entre los 20 y 40 años en individuos de raza blanca

Incidencia varía por sexo y grupo etáreo dependiendo de la infección primaria.

Representa menos del 2% de todas las espondiloartropatías*

Hasta un 50% de los pacientes pueden presentar secuelas

Ngaruiya, C. M (2013). A case of reactive arthritis: a great masquerader. *The Am. J. of eme med*, *31*(1), 266-e5.

Misra, R., & Gupta, L. (2017). Epidemiology: Time to revisit the concept of reactive arthritis. *Nature Reviews Rheumatology*, *13*(6), 327.

Epidemiología*

Se realizó una revisión sistemática donde se buscaba la incidencia de AR con patógenos entéricos revelando

Bacterias	Número de Casos/Infecciones
Campylobacter	9/1000
Salmonella	12/1000
Shigella	12/1000

Schmitt, S. K. (2017). Reactive arthritis. *Infectious Disease Clinics*, *31*(2), 265-277.

Microorganismos desencadenantes

Inciting agents of reactive arthritis

Common

Chlamydia trachomatis

Salmonella (several species)

Shigella (especially *S flexneri*)

Campylobacter jejuni

Yersinia (especially *Y enterocolitica* and *Y pseudotuberculosis*)

Uncommon

Neisseria gonorrhoea
Mycoplasma genitalium
Ureaplasma urealyticum
Clostridium difficile
Campylobacter lari
Chlamydia psittaci
Chlamydia pneumoniae

VIH

LPS

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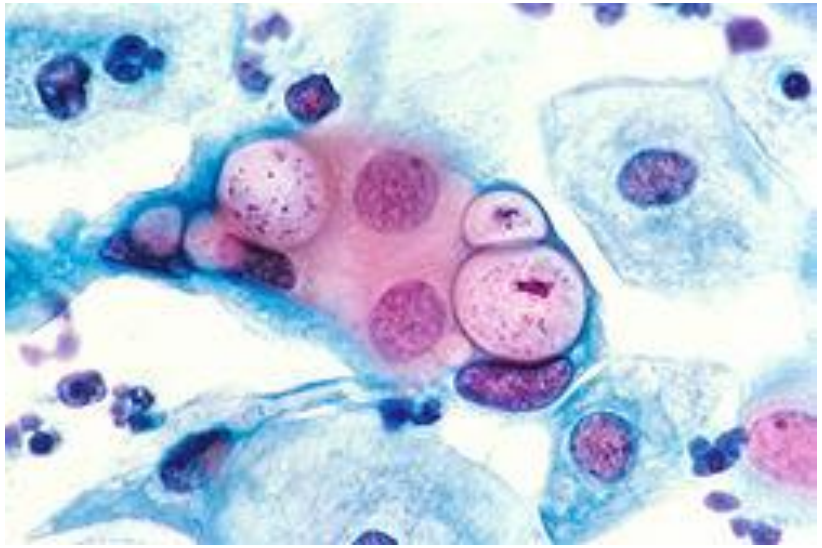
Goldsmith; Katz; Gilchrest. (2014). Fitzpatrick Dermatología 8Ed. Edit. Panamericana

Chlamydia trachomatis

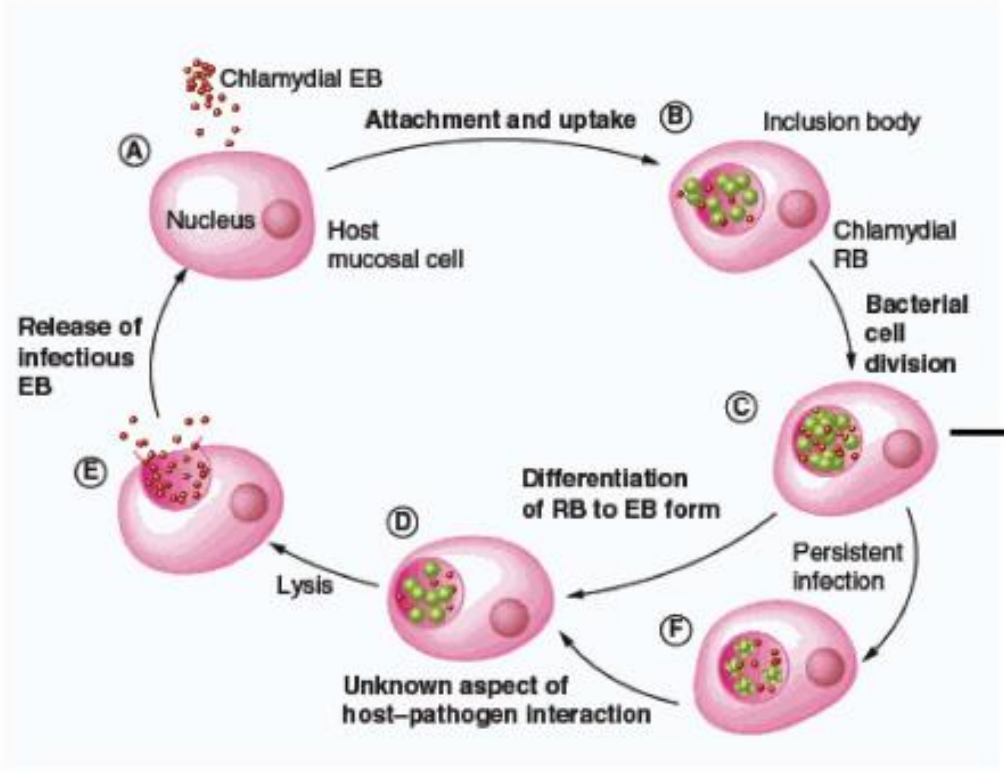
- Bacterias Gram -, IC obligadas, sin motilidad, replicación depende de las células huésped
- Puede infectar varios órganos
- Serovariedades de la A-K – Oculares + artritogénicas



Manifestations	*Chlamydia trachomatis*
(1) At the portal of entry of the infection	(A) *Urogenital female*: Urethral syndrome (frequency, dysuria), cervicitis (mucopurulent discharge, postcoital bleeding), endometritis/salpingitis (pelvic/abdominal pain, abnormal uterine bleeding, fever) *Male*: Urethritis (dysuria, urethral discharge), epididymitis (unilateral scrotal pain, swelling, tenderness), prostatitis (perineal discomfort, dysuria, frequency, urethral discharge), proctitis (rectal pain, bleeding, discharge, tenesmus, diarrhoea) (B) *Ocular*: Follicular conjunctivitis, neonatal ophthalmia (newborn), trachoma (endemic in developing countries) (C) *Pharyngeal and respiratory*: Tonsillitis, sore throat, sinusitis, bronchitis, atypical pneumonia (D) *Sequelae female*: Infertility, ectopic pregnancy, puerperal endometritis, adhesions around the uterine appendages, perihepatitis, periappendicitis *Male*: Urethral stricture

Zeidler, H., & Hudson, A. P. (2013). New insights into Chlamydia and arthritis. Promise of a cure?. *Annals of the rheumatic diseases*, annrheumdis-2013.

Chlamydia trachomatis



	C.trachomatis infection productive		persistent
morphology	EB/RB		aberrant forms
culture	+		-
metabolic activity	+		+
gene expression	+	MOMP	-
	+	HSP	+++
	+	LPS	+++
	+	enzymes for cytokinesis	-
	+	DNA replication	+
energy supply	+	glycolytic pathway	-
	+	ATP/ADP exchange	+

Zeidler, H., & Hudson, A. P. (2013). New insights into Chlamydia and arthritis. Promise of a cure?. *Annals of the rheumatic diseases*, annrheumdis-2013.

Factores del huésped*

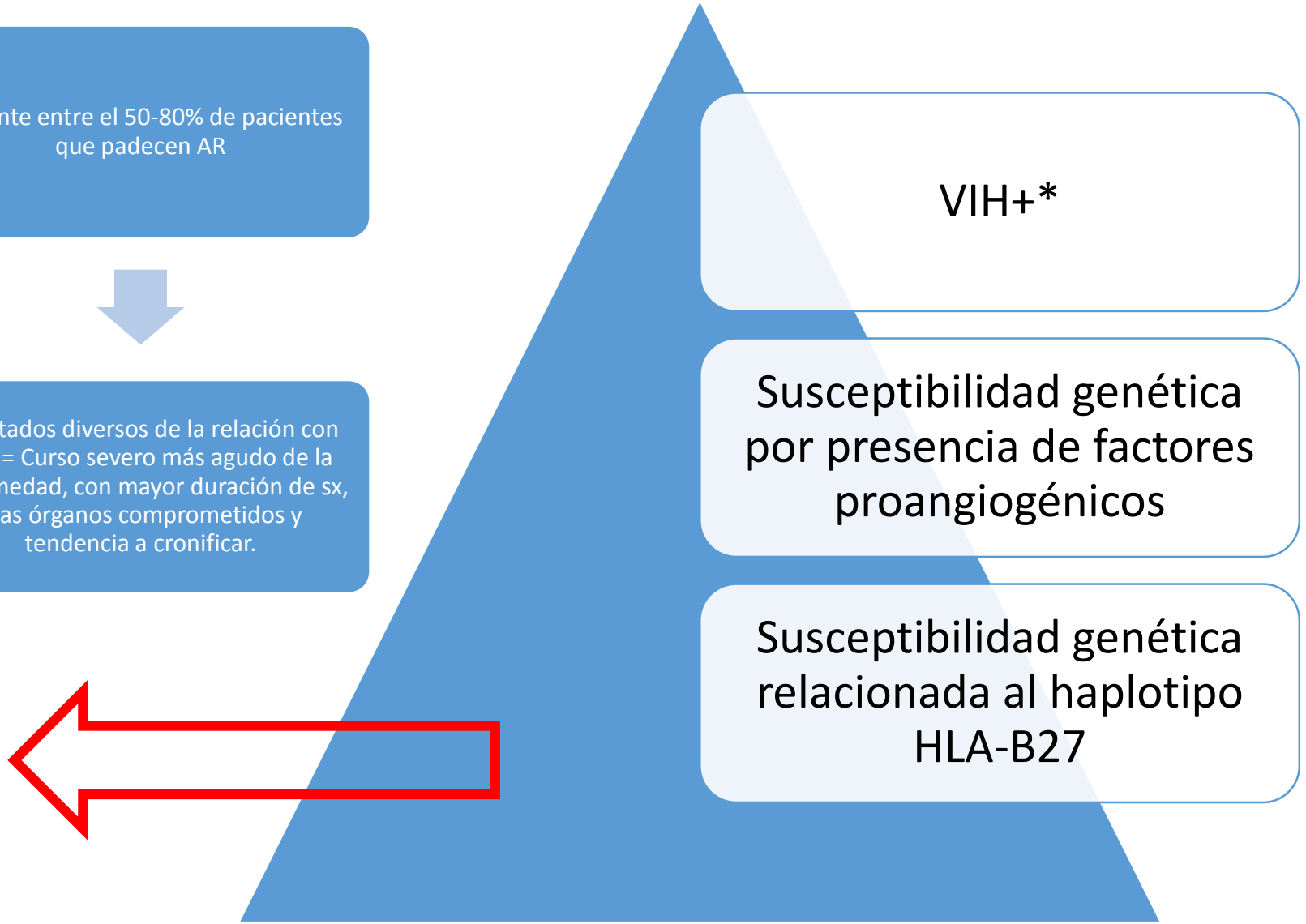
Presente en el 7-9% de las personas de raza blanca

Presente entre el 50-80% de pacientes que padecen AR

Resultados diversos de la relación con AR* = Curso severo más agudo de la enfermedad, con mayor duración de sx, mas órganos comprometidos y tendencia a cronificar.

El alelo observado con mayor frecuencia en pacientes con AR es HLA-B*2705 *

La mayoría de estudios de los pacientes con AR + HLA-B27 la desarrollan posteneritis*



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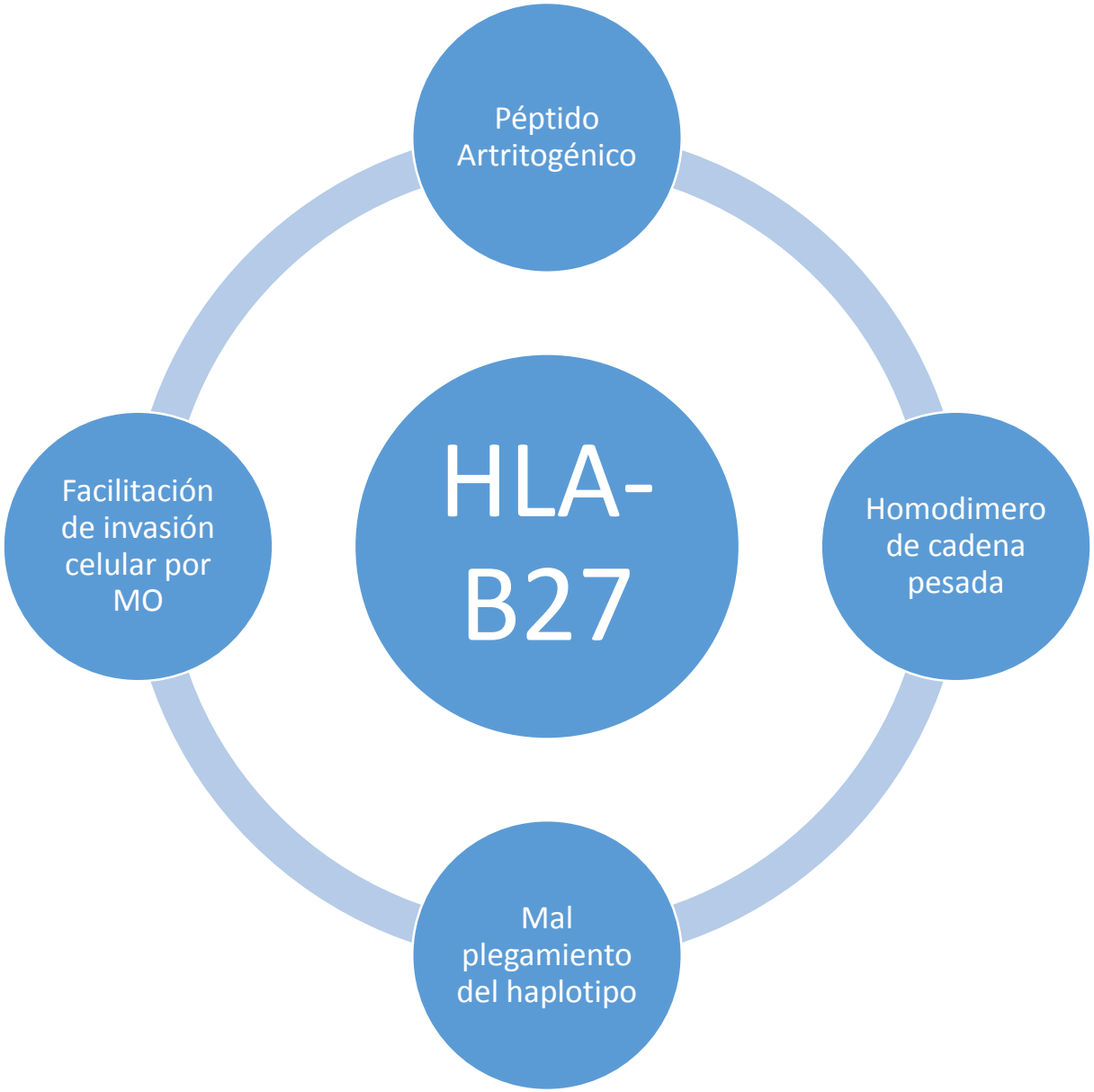
Fisiopatología*

Persistencia de bacterias o PDB en la articulación	• Interacción estructurada de factores microbianos y diversas serovariedades de MO
El tipo de interacción huésped- patógeno	• Mecanismos subyacentes específicos de incorporación celular del MO y migración desconocidos • Disbalance Microbioma • Polimorfismos TRL
La respuesta inmune local dirigida a estas bacterias	• Disbalance Th1/Th2 • Respuesta Th17 aumentada

García-Kutzbach, A., Chacón-Súchite, J., (2018). Reactive arthritis: update 2018. *Clinical rheumatology*, 1-6.



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Manifestaciones clínicas*

El dx incorrecto
=
Subdiagnóstico

- Espectro clínico variable pero manifestaciones clínicas similares*
- Afectación de múltiples órganos*
- Fase aguda*
- Fase crónica*

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Manifestaciones musculoesqueléticas

- Aparecen por lo general cuando ya no hay infección primaria activa
- Los individuos afectados pueden evolucionar hacia una artritis inflamatoria*
- Formas atípicas de AR???

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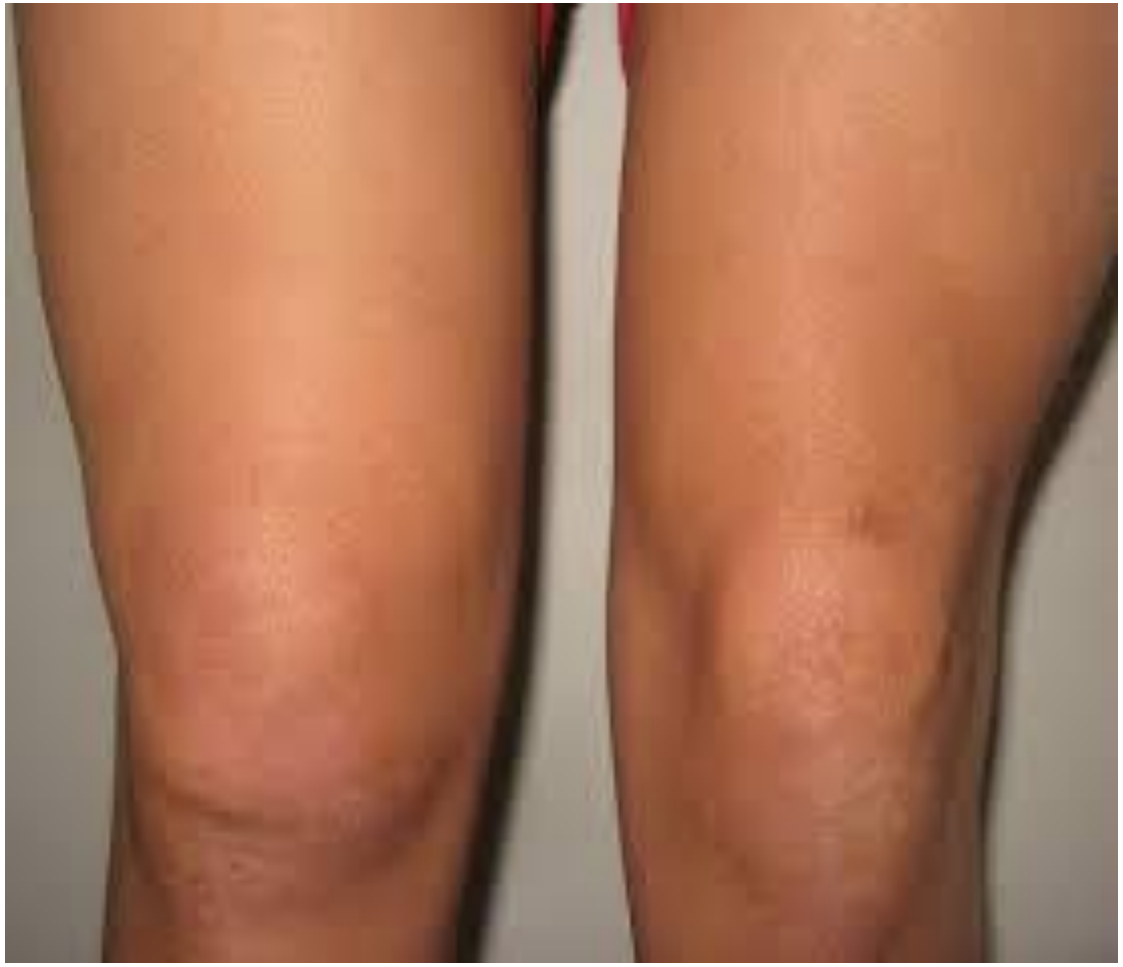
Compromiso articular periférico

100%



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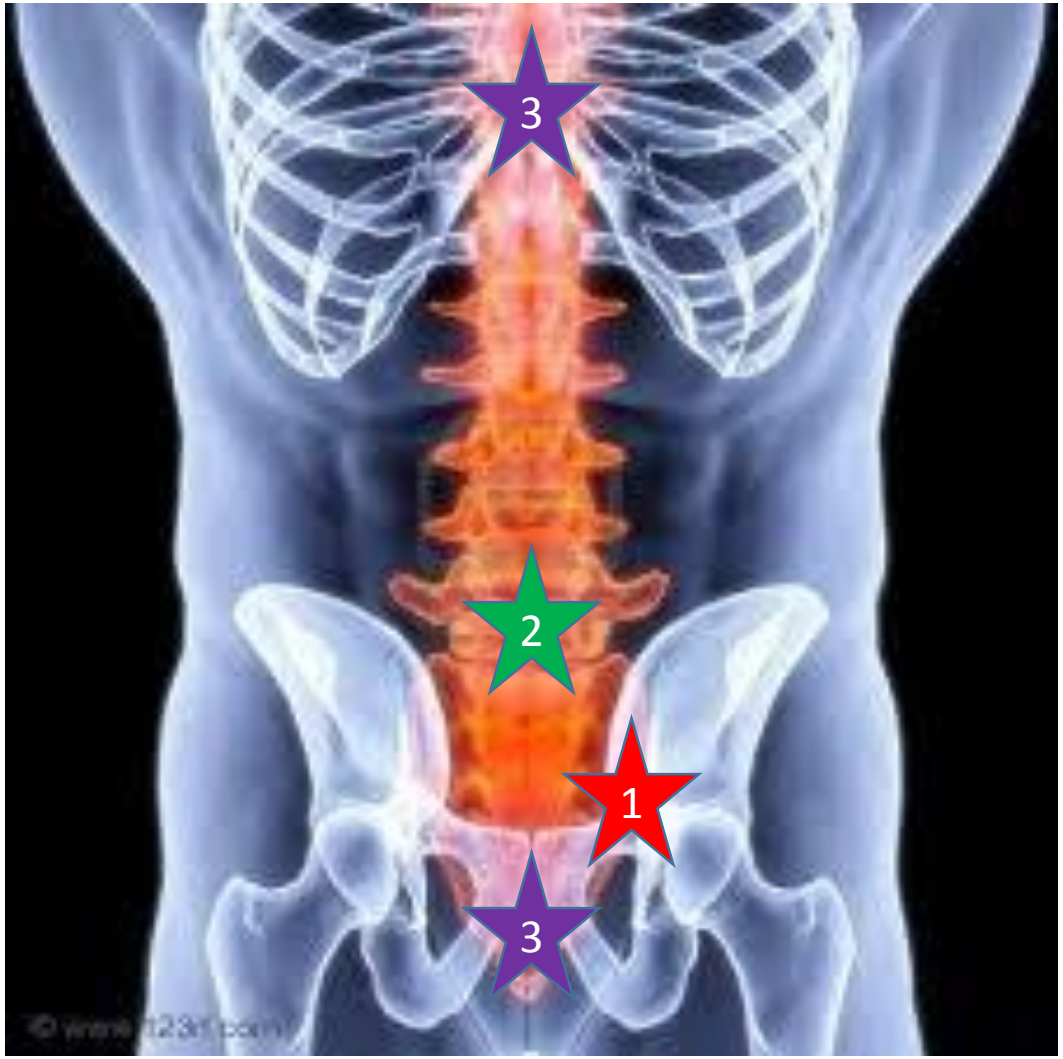
Compromiso articular axial

15-30%



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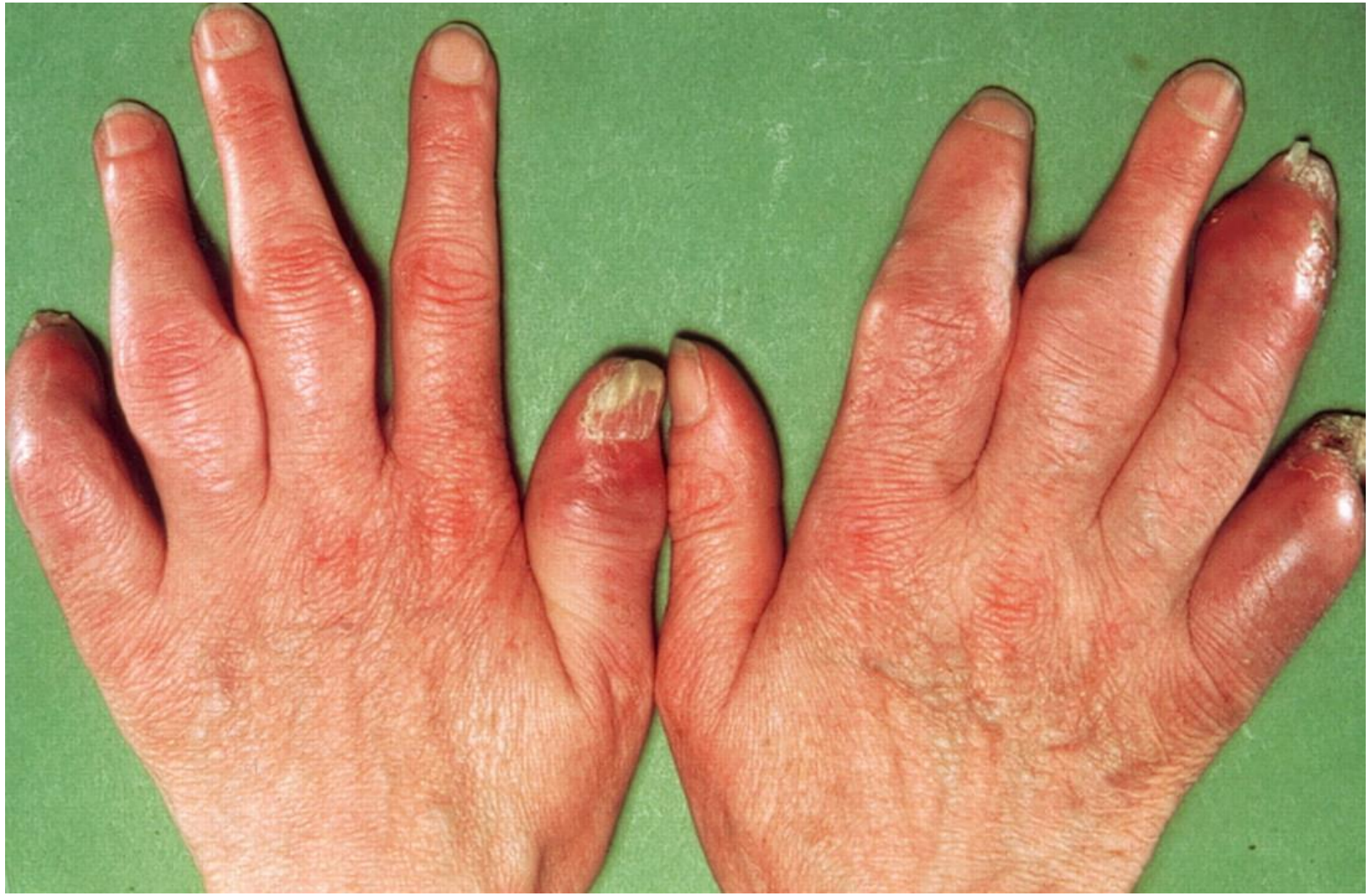
Dactilitis

16-40%



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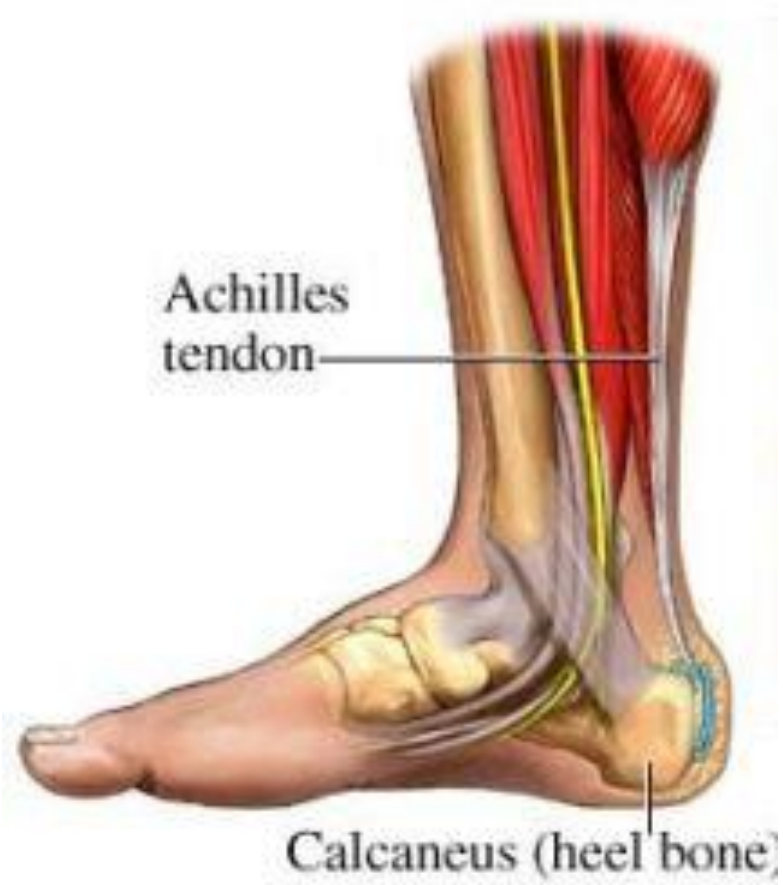
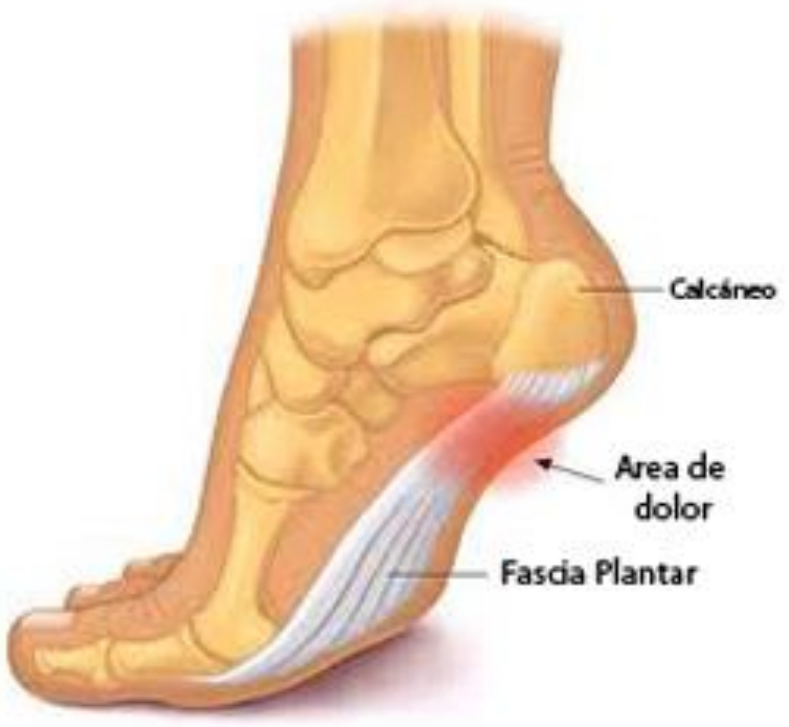
Entesitis

20-40%





Schmitt, S. K. (2017). Reactive arthritis. *Infectious Disease Clinics*, *31*(2), 265-277.

Para recordar…

Musculoskeletal manifestations of reactive arthritis

Peripheral

Monoarthritis or asymmetric > symmetric oligoarthritis (especially large joints of lower extremities)

Enthesitis (tendon/bone insertion points—Achilles tendonitis or plantar fasciitis > knees or upper extremities)

Dactylitis (sausage digit fingers or toes)

Axial

Spine (lumbar > thoracic/cervical)

Sacroiliac joints

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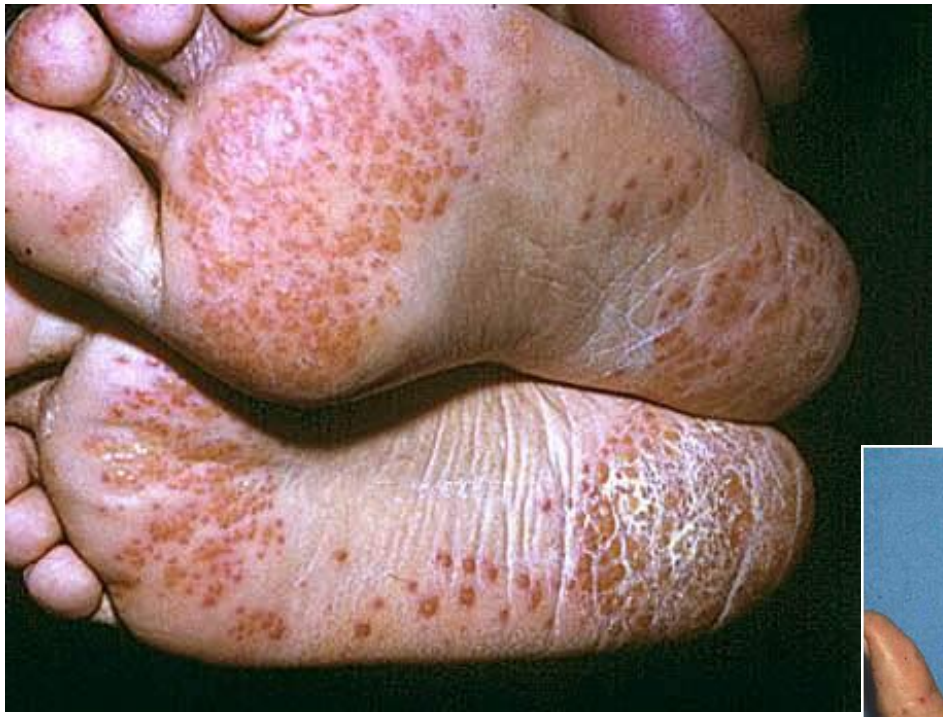
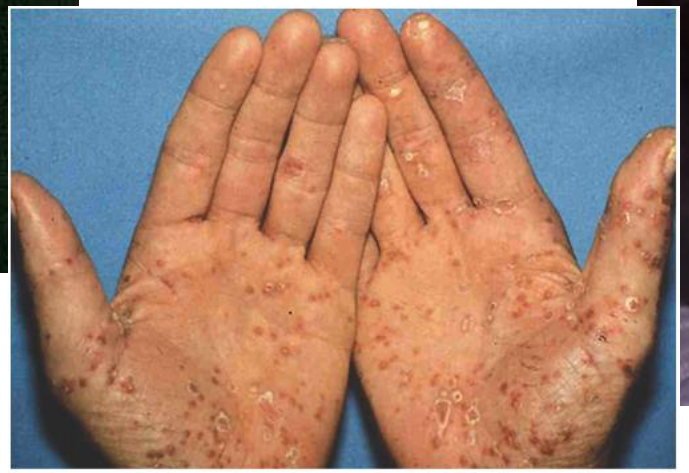
Manifestaciones extrarticulares

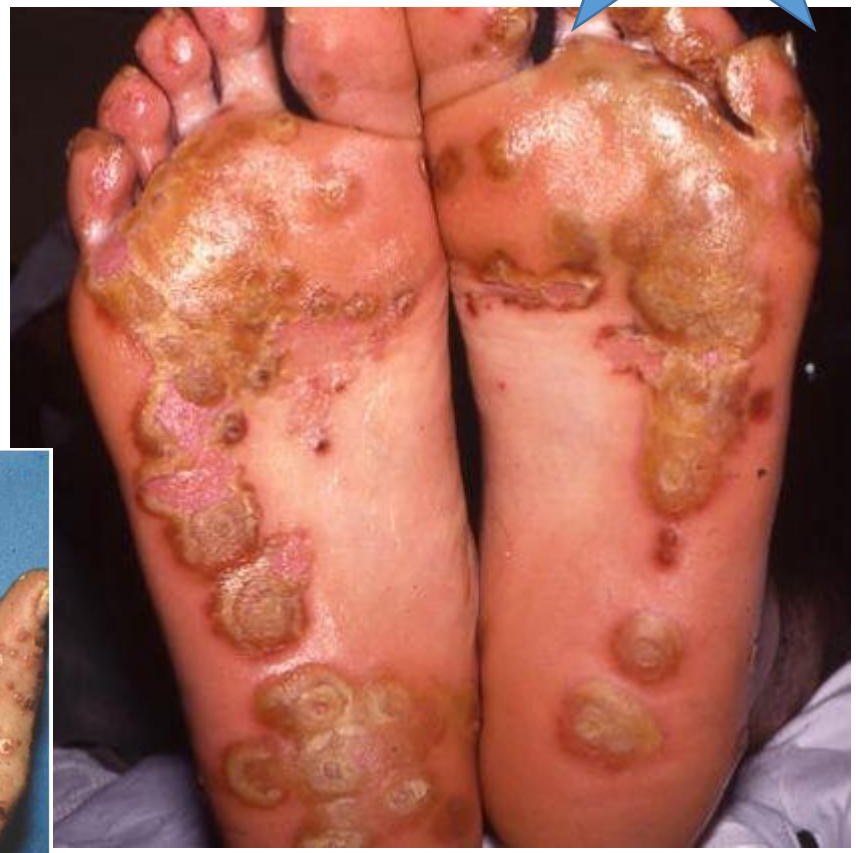
- No son raras particularmente en el escenario de una infección del TGU
- Los principales órganos afectados son la piel, anexos, los ojos, la uretra
- Menor afectación renal y cardiáca

Queratodermia blenorrágica

33%







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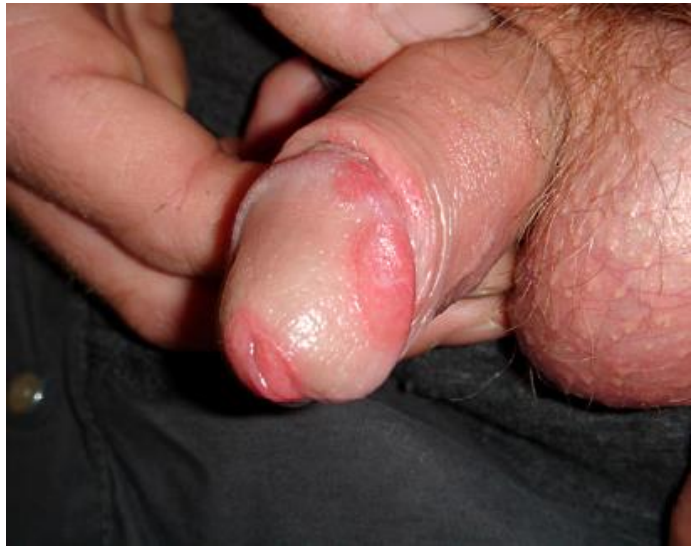
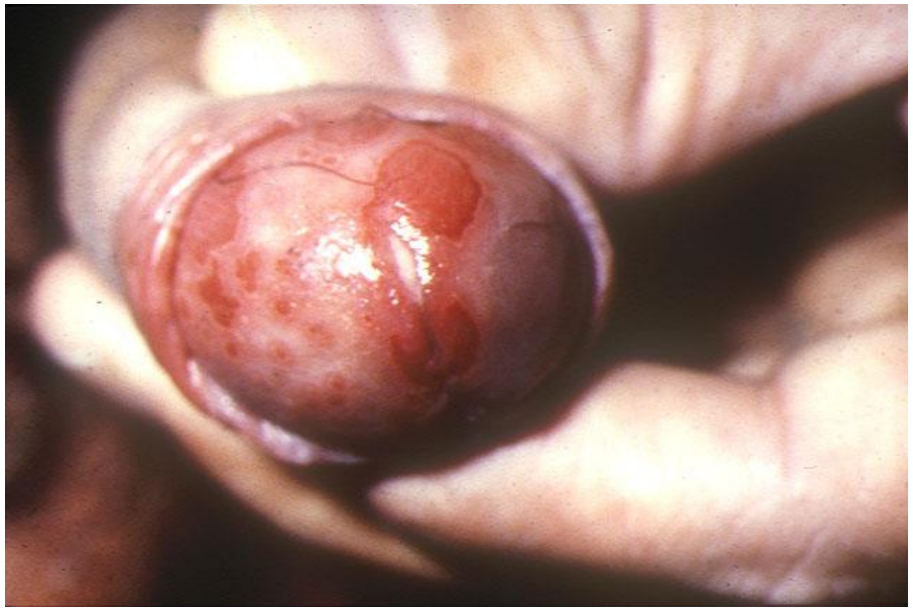
Balanitis circinada



14-50%



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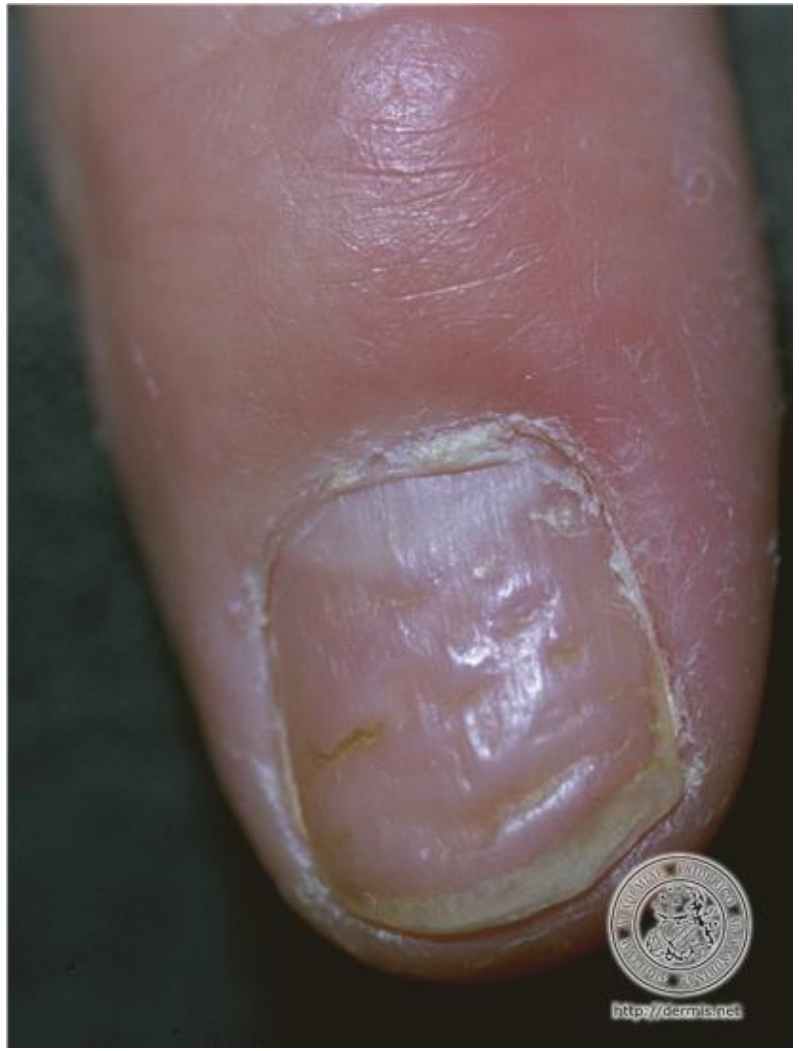
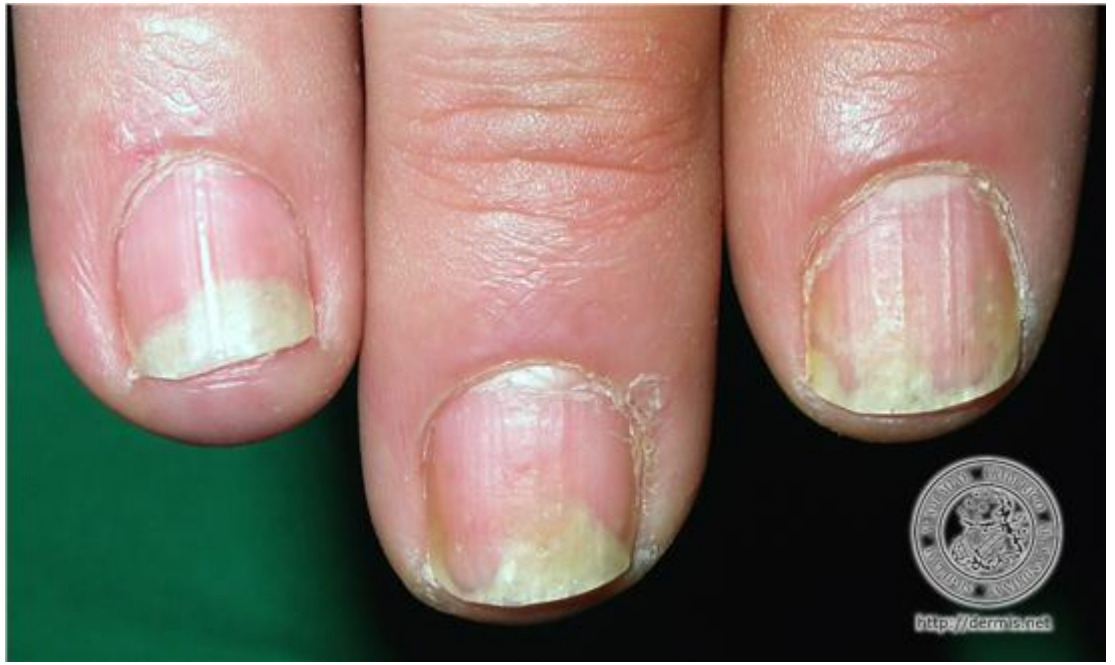
Afectación ungular

20-30%





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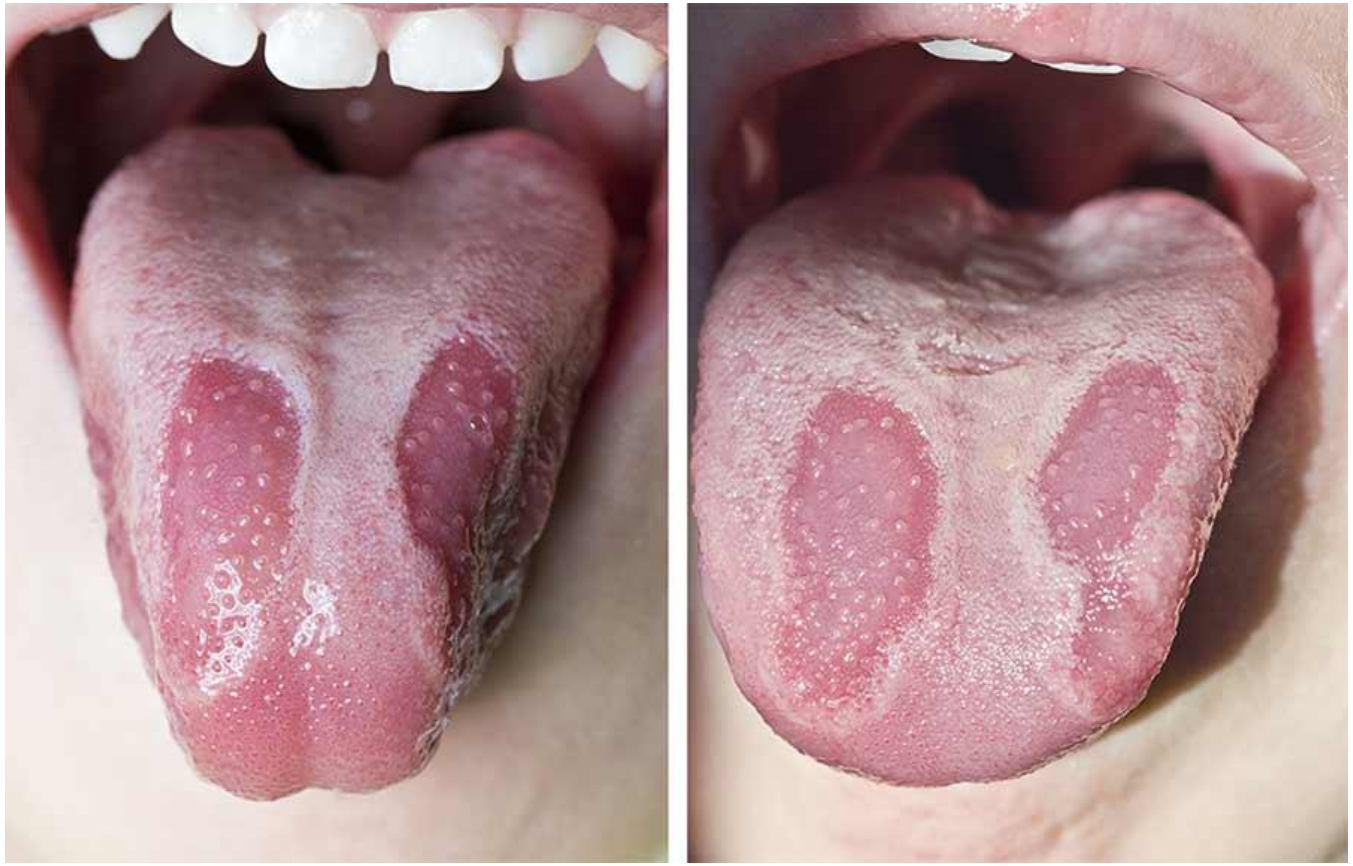
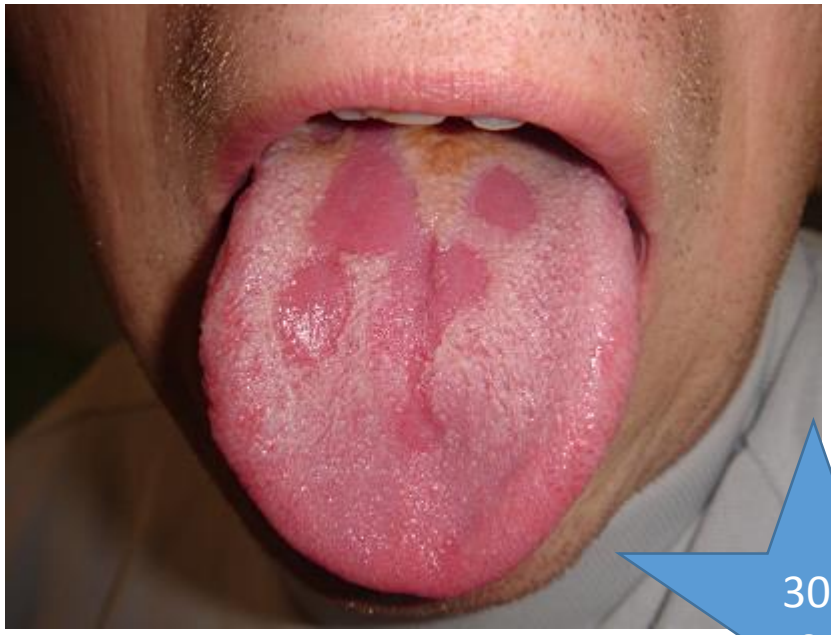
Afectación de mucosas – Lengua geográfica





30-50%

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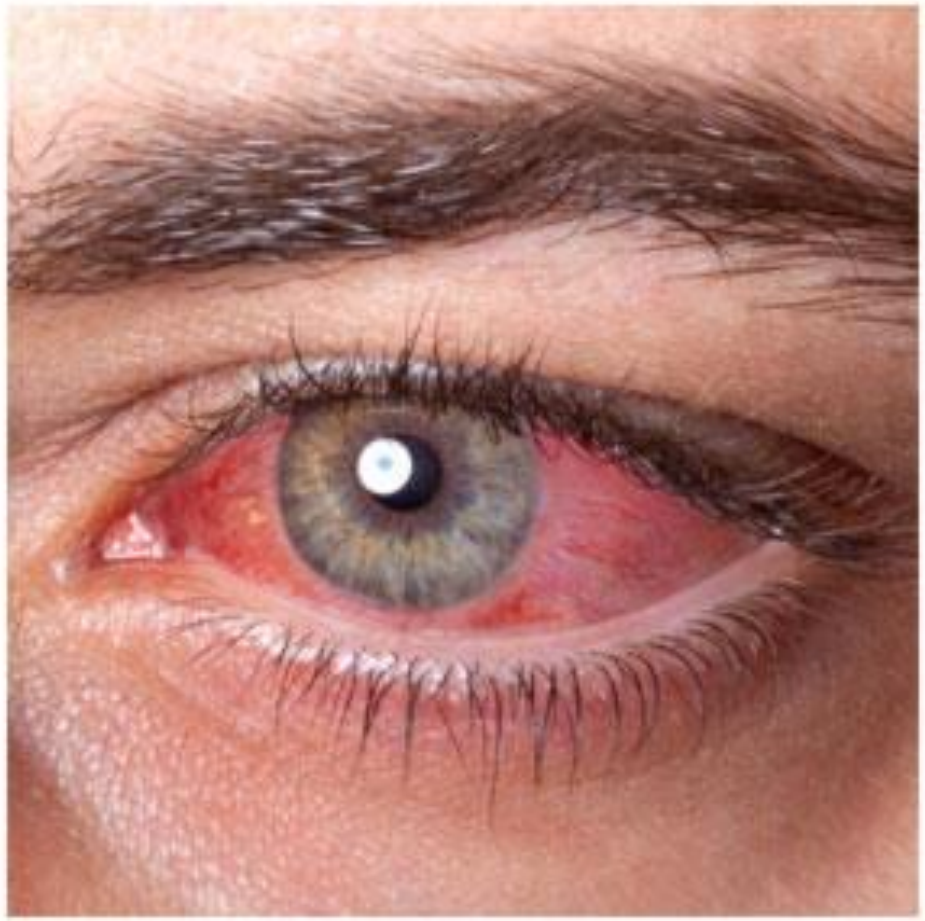
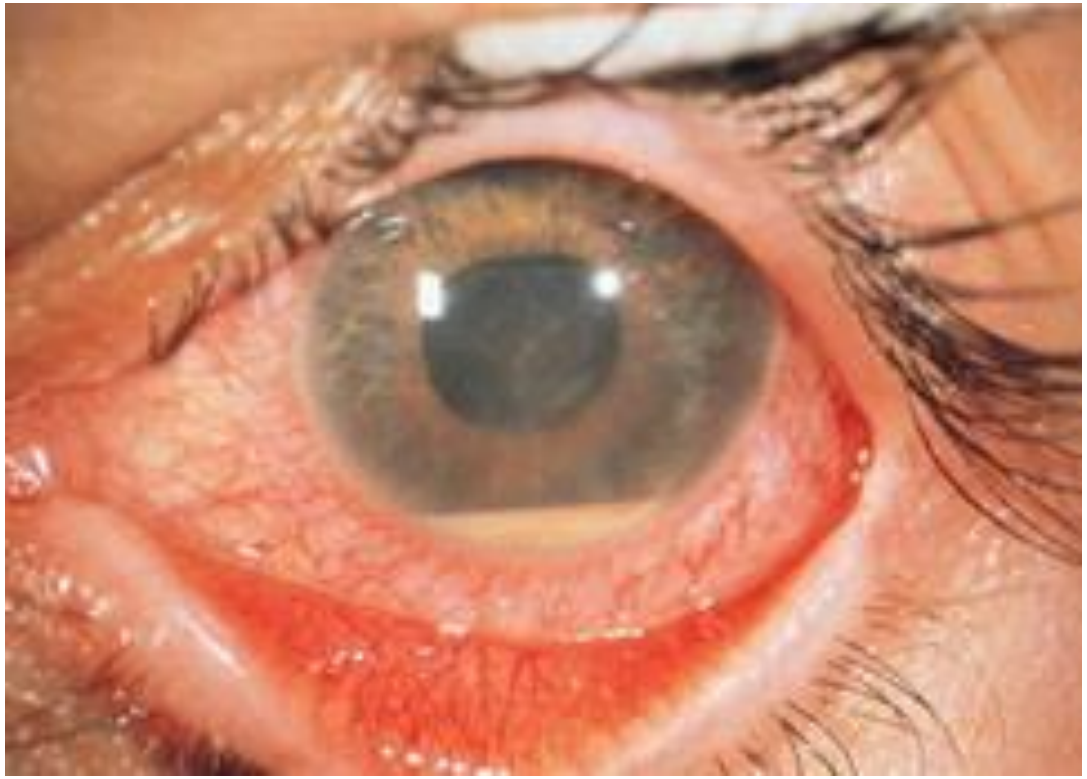
Conjuntivitis / Uveítis

30-60%





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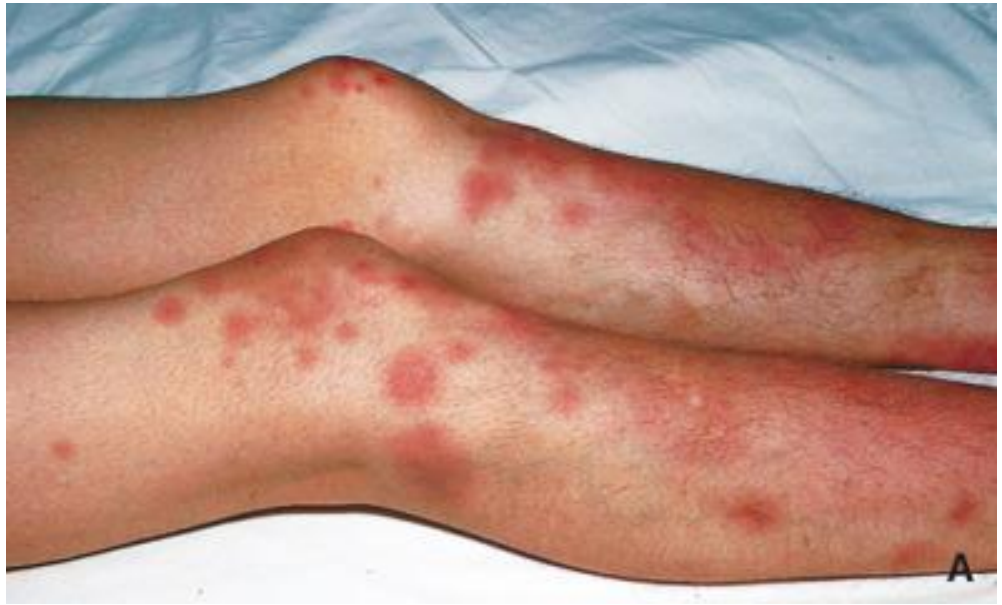
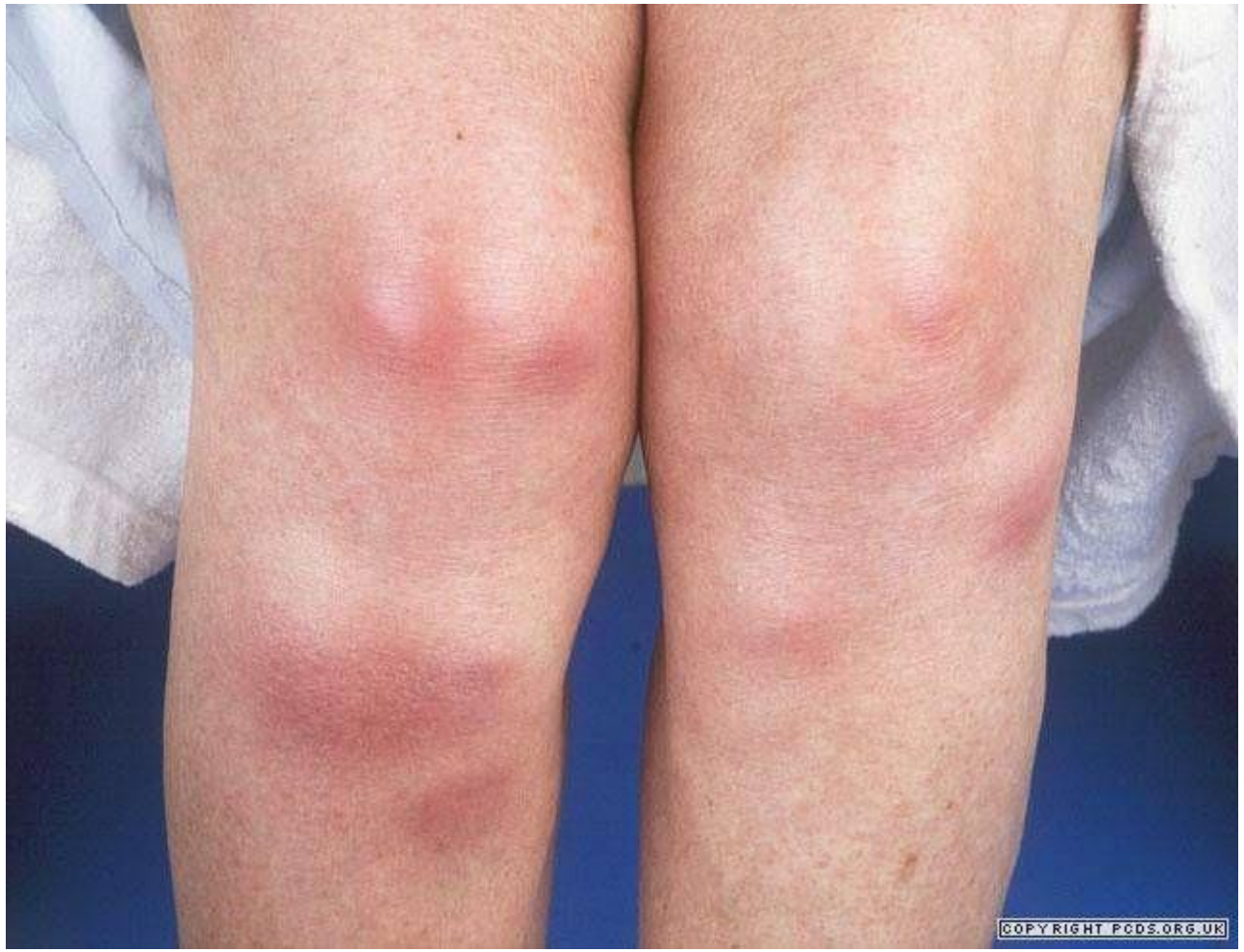
Eritema nodoso





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Otras compromisos menos comunes…

Box 1. Rare clinical features

Cardiac:

- left ventricular dilatation, pericarditis, aortic valve disease.

Renal:

- glomerulonephritis, IgA nephropathy.

Neurological:

- meningoencephalitis, nerve palsies.

Other:

- thrombophlebitis, subcutaneous nodules.

Carlin, E., & Flew, S. (2016). Sexually acquired reactive arthritis. *Clinical Medicine*, *16*(2), 193-196.

Para recordar…

Extraarticular manifestations of reactive arthritis

Genitourinary: Urethritis, cervicitis, salpingo-oophoritis, cystitis, prostatitis

Mucous membranes: Painless oral ulceration

Cutaneous: Keratoderma blennorrhagica, circinate balanitis, erythema nodosum

Ophthalmologic: Conjunctivitis, keratitis, episcleritis, or anterior uveitis

Cardiac: Aortic valvular insufficiency, pericarditis, heart block

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Diagnóstico diferencial

DOI: 10.1111/jdv.12741 JEADV

REVIEW ARTICLE

Reactive Arthritis

P.G. Stavropoulos, E. Soura,* A. Kanelleas, A. Katsambas, C. Antoniou

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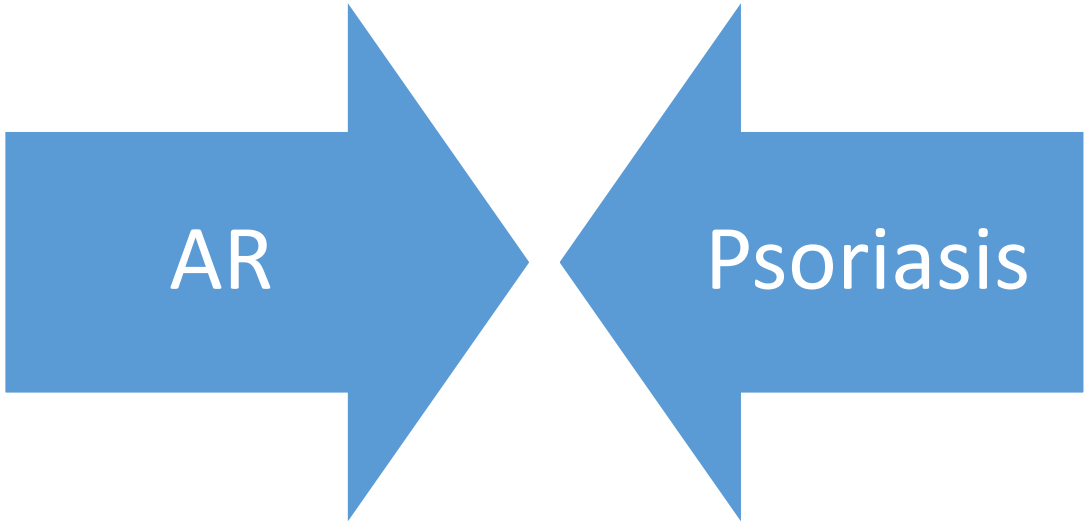
*Correspondence: E. Soura. E-mail: anonaki@hotmail.com



		Reactive Arthritis	Psoriasis
Genetics	HLA-B27	80%	40% (in PsA patients mainly)
	PSORS1-9	No	Yes
	TNF-a polymorphisms	TNFa-238	TNFa-238 (only in PsA)
		Other TNF-α polymorphisms: poorly described	A constellation of TNF-α polymorphisms depending on the type of psoriasis/co-morbidities
Pathogenesis		Remains to be fully elucidated	Extensively researched
	Associated TLRs	TLR-2, TLR-4	Mainly TLR-7,-8,-9
	Infection	Always. Pathogen persistence is a prerequisite	In some instances. Pathogen persistence is not a feature
	Molecular mimicry	Multiple autoantigens have been described, but not one common to all pathogens	Protein M (β-haemolytic streptococcus) has been associated
	T cells	Th2/Th1 imbalance has been described (type 2 immune reaction dominance)	Mainly Th17, Th1
	Keratinocyte role	Unknown-not described	Multiple genetic-molecular alterations have been described
Age of onset		Late teens to early adulthood	• Bimodal distribution (Psoriasis) • 35–45 years (PsA)
Male to female ratio		5 : 1	1 : 1
Arthritis	Peripheral arthritis	Mainly in lower limbs	May involve all joints
	Sacroilitis	60%	40% (PsA)
	Enthesitis	Yes	Yes (PsA)
	Dactylitis	Yes	Yes (PsA)
Ocular manifestations		Acute anterior uveitis	Chronic uveitis
		Conjunctivitis	No conjuctivitis

Stavropoulos, P. G., Soura, E., Kanelleas, A., Katsambas, A., & Antoniou, C. (2015). Reactive arthritis. *Journal of the European Academy of Dermatology and Venereology*, *29*(3), 415-424.

Skin manifestations	Typical plaques of psoriasis	No	Yes
	Pustular lesions of palms and soles	Keratoderma blennorhagicum	Palmoplantar pustular psoriasis
		No typical psoriasis plaques on other body sites	Typical psoriasis plaques on other body sites or previous history of psoriasis vulgaris
		Histology: numerous pustules, massive hyperkeratosis	Histology: pustules, hyperkeratosis less prominent than in KB
	Nails	Onycholysis: yes	Onycholysis: yes
		Onychodystrophy: yes	Onychodystrophy: yes
		Nail pitting: very rare	Nail pitting: typical/ very common
		Splinter haemorrhage, Oil drop: not found	Splinter haemorrhage, Oil drop: typical/ very common
	Genital Lesions	Circinate balanitis/vaginal lesions	Psoriasis of the genital area
		40% of patients	7% of Ps patients
		Erythematous lesions, shallow ulcers, centrifugal distribution	Similar clinical picture with CB but: scaling may be present, no centrifugal distribution
		Equally common in males and females	Rare in females
		No koebner phenomenon present	Koebner phenomenon present
		No Auspitz sign	Auspitz sign may be present in keratotic areas
		Histology: Similar to psoriasis, subtle hyperkeratosis and parakeratosis	Histology: Typical for psoriasis, more prominent hyperkeratosis and parakeratosis compared to CB
	Oral mucosa	Geographic tongue: yes	Geographic tongue: yes
		Fissured tongue: not observed	Fissured tongue: typical
		Oral erosions: typical	Oral erosions: not observed
		Circinate lesions: typical	Circinate lesions: not observed
	Erythema nodosun	Rarely present	Never

Stavropoulos, P. G., Soura, E., Kanelleas, A., Katsambas, A., & Antoniou, C. (2015). Reactive arthritis. *Journal of the European Academy of Dermatology and Venereology*, *29*(3), 415-424.

Diagnóstico

Recently, European guidelines on the management of sexually acquired ReA were published[45]. The diagnosis is based on three components:

1. recognition of the typical features of spondyloarthritis,
2. demonstration of the evidence of genitourinary infection
3. investigation of specificity and activity of arthritis.

Major criteria	1) Arthritis with 2 of 3 of the following findings: - Asymmetric - Mono or oligoarthritis - Lower limb involvement 2) Preceding symptomatic infection with 1 or 2 of the following findings: - Enteritis (defined as diarrhea for at least 1 day, and 3 days to 6 weeks before the onset of arthritis) - Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)
Minor criteria	At least one of the following: 1) Evidence of triggering infection: - Positive urine ligase reaction or urethral/cervical swab for *Chlamydia trachomatis* - Positive stool culture for enteric pathogens associated with reactive arthritis 2) Evidence of persistent synovial infection (positive immunohistology or PCR for *Chlamydia*)

Selmi, C., & Gershwin, M. E. (2014). Diagnosis and classification of reactive arthritis. *Autoimmunity reviews*, *13*(4-5), 546-549.

Aislamiento e identificación del patógeno

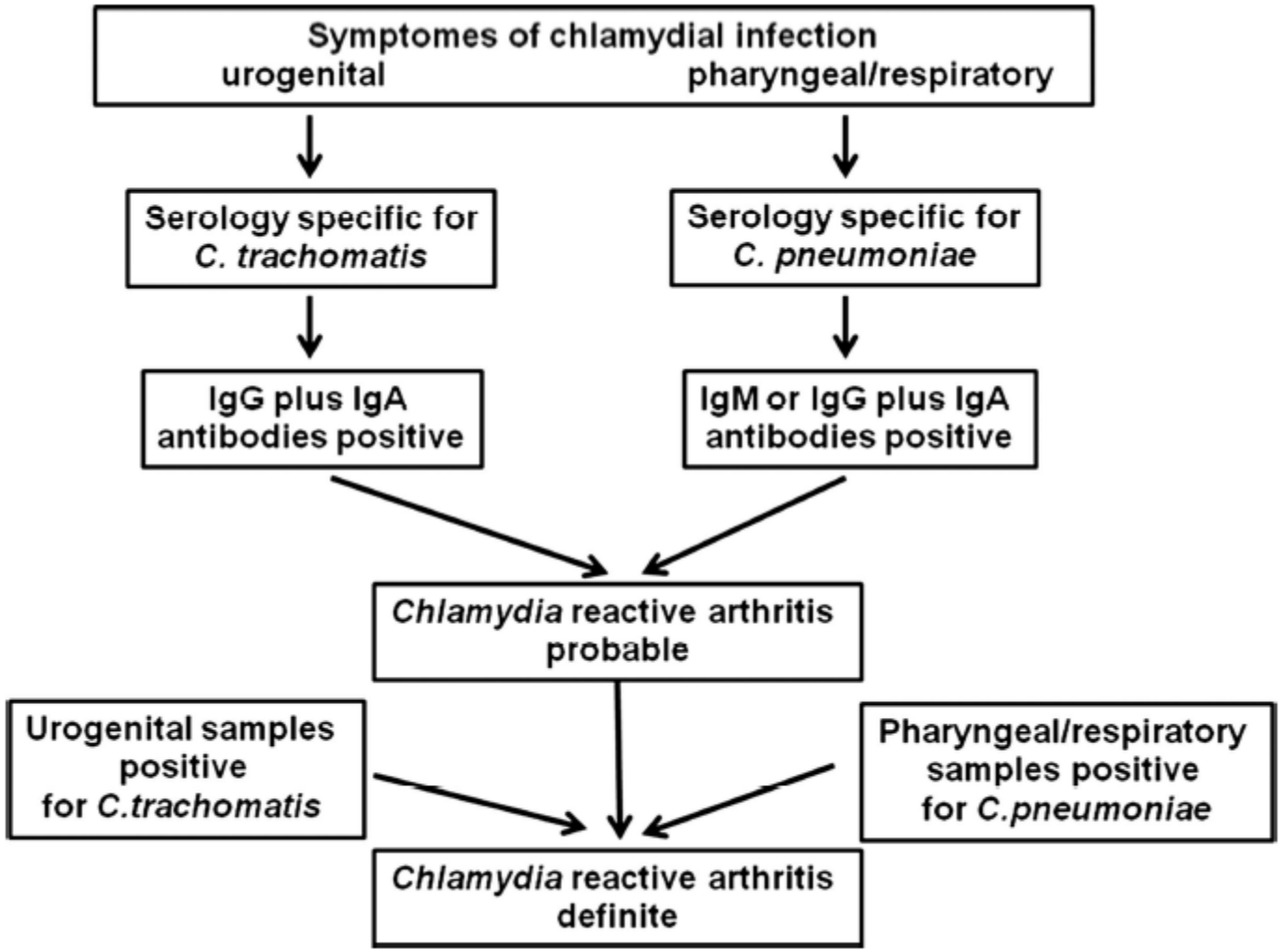
No hay un panel definitivo de laboratorio establecido

Tipo de infección	Fase infecciosa aguda	Fase postinfecciosa
Entérica	Cultivo MF	Ac específicos en suero
Genitourinaria	PCR orina o muestra escobillón de uretra	Ac específicos en suero // Muestra líquido sinovial - PCR

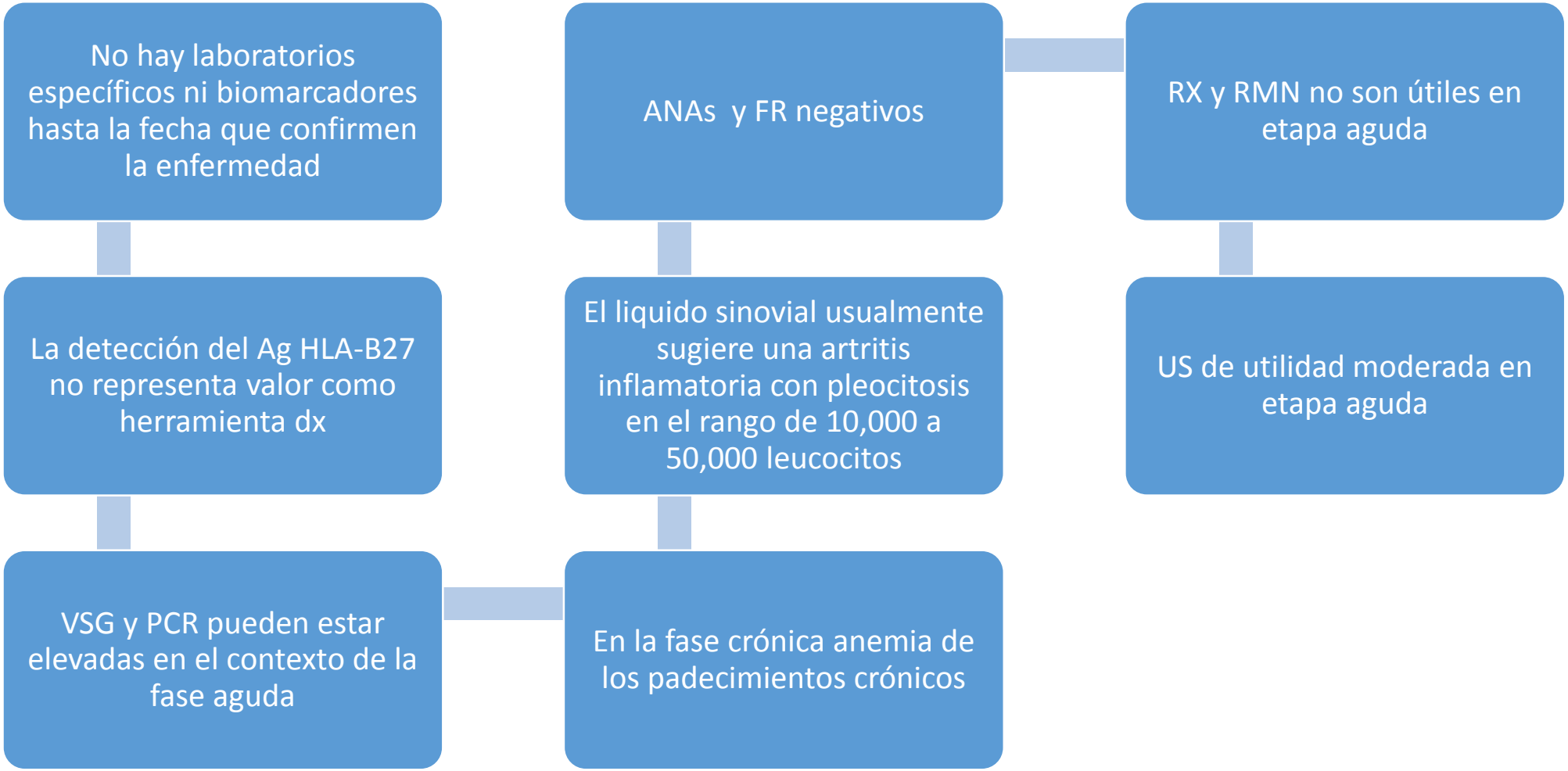
Reactividad cruzada!!!

Selmi, C., & Gershwin, M. E. (2014). Diagnosis and classification of reactive arthritis. *Autoimmunity reviews*, *13*(4-5), 546-549.

Algoritmo / Serología -Chlamydia



Otros paraclínicos



Carlin, E., & Flew, S. (2016). Sexually acquired reactive arthritis. *Clinical Medicine*, *16*(2), 193-196.

Tratamiento

Manejo de infección aguda

- TGU: Chlamydia? = Azitromicina 1gr oral Du o Doxiciclina 100mg Bid x 7 días
- TGI: Gral/ autolimitadas pero en pctes con Ant AR pueden usarse A/B orales.*

Fase aguda*

- AINES 2 sem

  Gastritis? = COX-2 + Inh Bomba Protones
- CE intralesionales en articulaciones con persistencia de signos y síntomas

1st **non-steroidal anti-inflammatory drug (NSAID)**

» No NSAID has been shown to be superior to any other in reactive arthritis (ReA).

» Expert opinion suggests trying indometacin and naproxen as first-line agents, although many others are available and may be equally effective.

Primary options

» indometacin: 25 mg orally two to three times daily when required

OR

Primary options

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

Primary options

» ibuprofen: 300-400 mg orally three to four times daily when required, maximum 2400 mg/day

OR

Primary options

» diclofenac potassium: 50 mg orally (immediate-release) twice or three times daily when required

OR

Primary options

» diclofenac sodium: 100 mg orally (extended-release) once daily when required

Schmitt, S. K. (2017). Reactive arthritis. *Infectious Disease Clinics*, *31*(2), 265-277.

García-Kutzbach, A., Chacón-Súchite, J., García-Ferrer, H., & Iraheta, I. (2018). Reactive arthritis: update 2018. *Clinical rheumatology*, 1-6.

Tratamiento

Refractario?*

- Sulfazalasina: 2g/d por 3 meses*
- Metotrexate 7,5-15mg semana hasta 25mg si resistente
- CE orales*
- Anti-TNF*
- Anti –IL17

Lesiones cutáneas

- Leves = No Tto
- Moderadas = Queratolíticos, CE tópicos, Analogos de la Vit D3
- Severos = Metotrexate dosis bajas, retinoides orales, o Anti-TNF

Primary options

» sulfasalazine: 500 mg orally once daily initially, increase by 500 mg/day increments at weekly intervals according to response, maximum 2 g/day given in 2-3 divided doses

Primary options

» prednisolone: 0.5 to 1 mg/kg/day orally, taper dose gradually as soon as practical

Schmitt, S. K. (2017). Reactive arthritis. *Infectious Disease Clinics*, *31*(2), 265-277.

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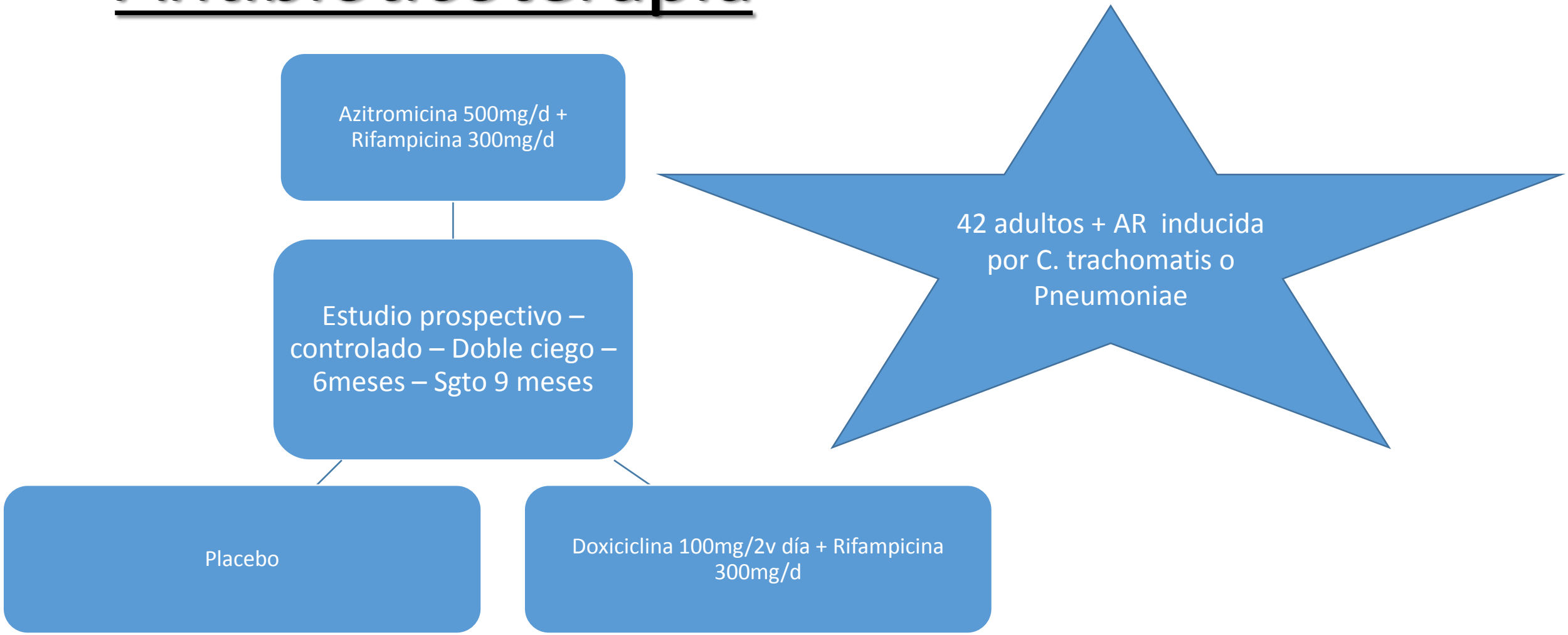
Antibioticoterapia



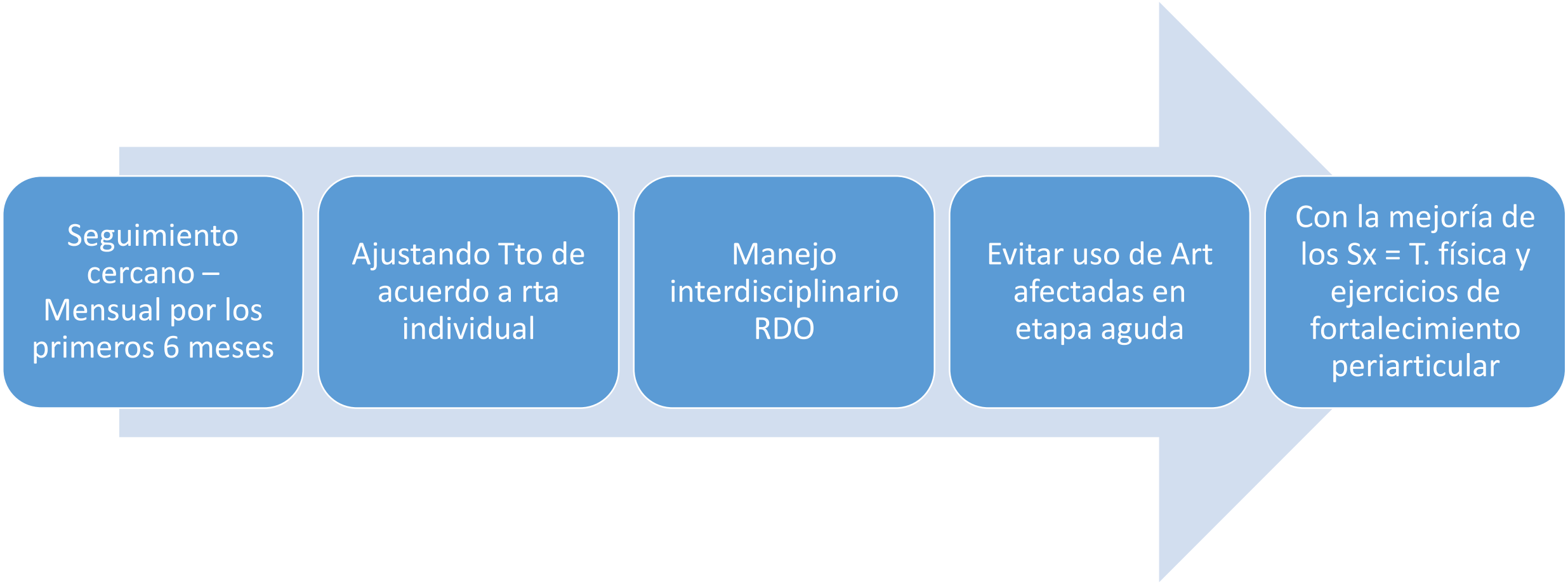
Carter, J. D., Espinoza, L. R., Inman, et.al (2010). Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. *Arthritis & Rheumatism*, *62*(5), 1298-1307.

Antibioticoterapia

- Ambas combinaciones superiores a placebo
- Mejoría de sx articulares 63% Vs 20% y Remisiones 22% Vs 0%
- Alta probabilidad de eliminación de infección persistente = Cura??
- P=0,01 y NNT 3

Carter, J. D., Espinoza, L. R., Inman, et.al (2010). Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. *Arthritis & Rheumatism*, *62*(5), 1298-1307.

Monitoreo y recomendaciones



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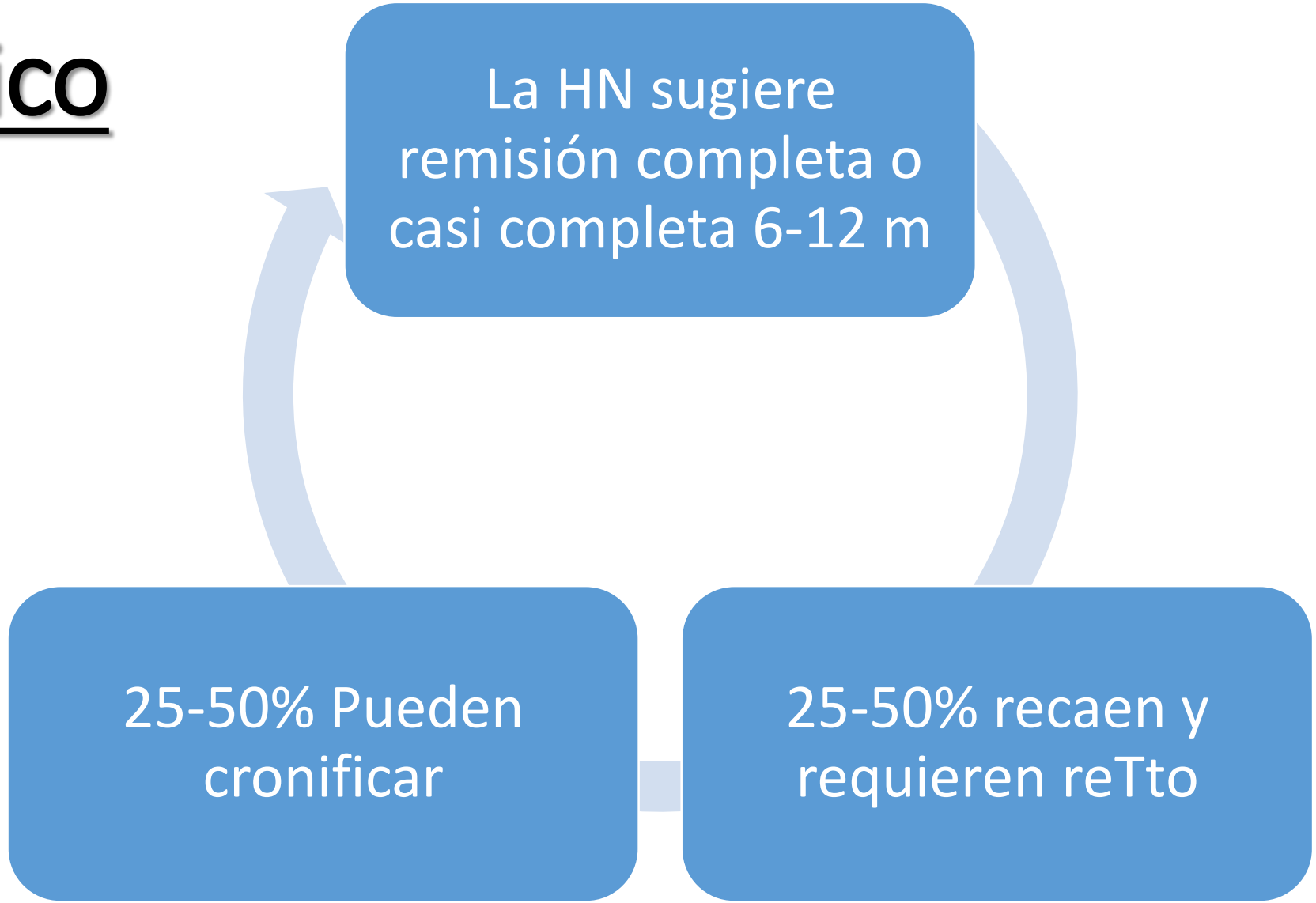
Pronóstico



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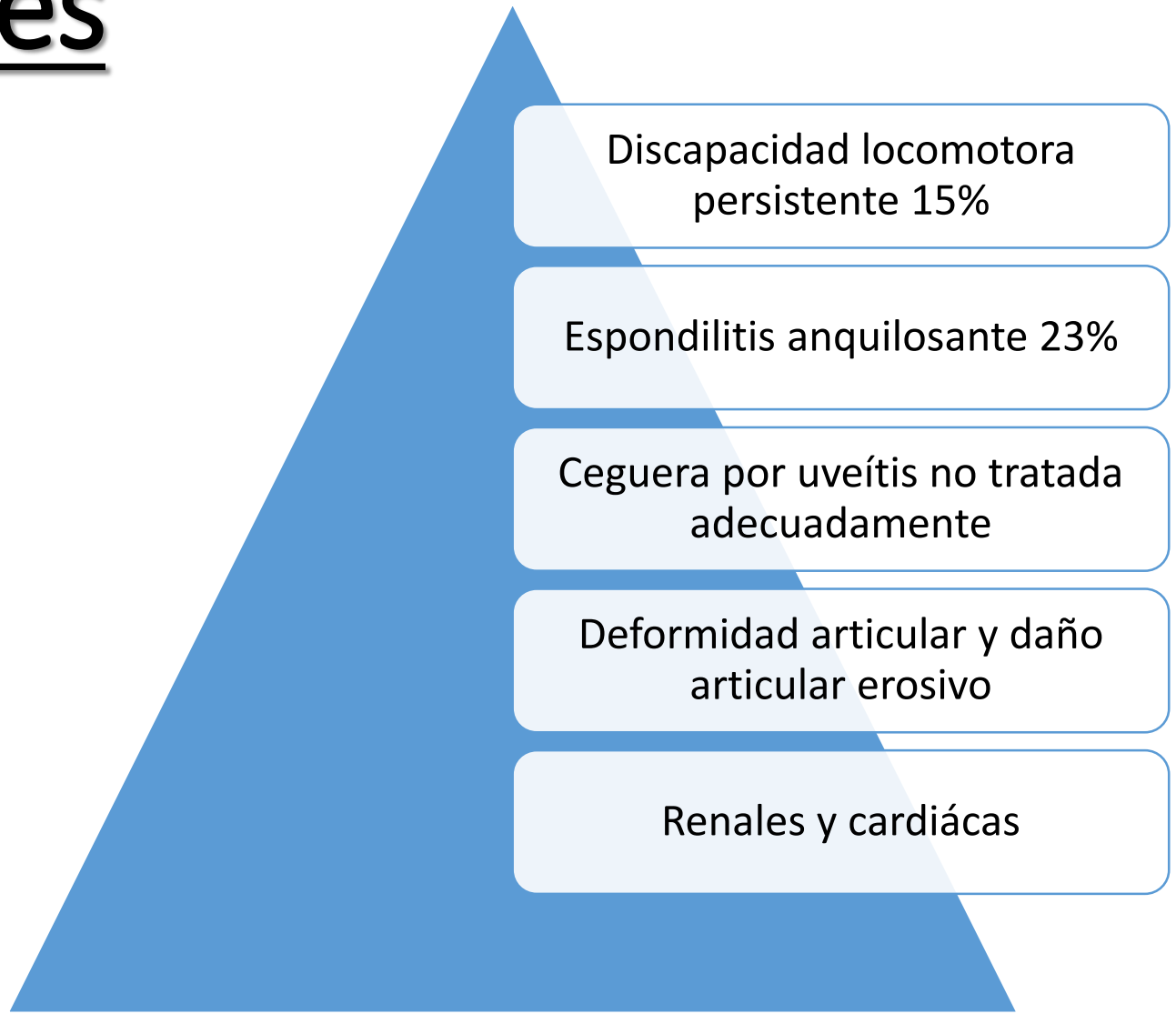
Complicaciones



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Conclusiones

Enfermedad de etiopatogenia enigmática

Compromiso articular inflamatorio axial oligoarticular asimétrico, de piel, mucosas y ojos.

Diagnostico clínico: Signos y Síntomas + evidencia objetiva de infección previa

Tratamiento principal con AINES

Pronóstico Variable – Puede cronificar

GRACIAS!!!