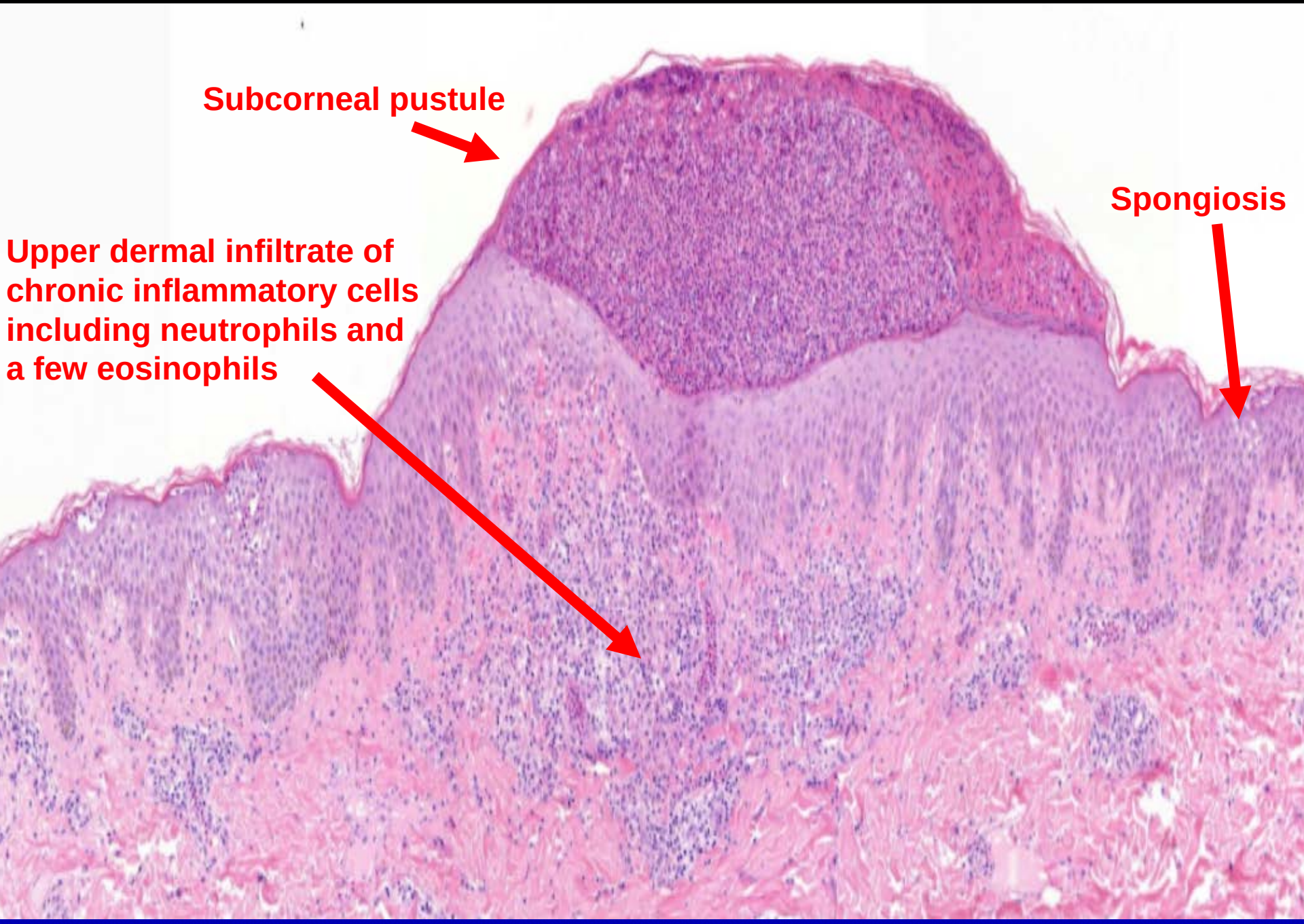
Miss DS 16/12/88, Aged 29

- Holidayed in Bangla Desh 23/11/16 for 1 month
- D&V for 3 days
- Well on return from UK
- 12/2/17 Fever, shivery, cough, body pain
- 19/2/17 Treated with Cefixime for 1 week + Lemsip (Paracetamol and Phenylephrine)
- 10 days later rash appeared on trunk, gradually extended

- No personal or family history of psoriasis


Subcorneal pustule
Spongiosis
Upper dermal infiltrate of chronic inflammatory cells including neutrophils and a few eosinophils

Investigations

- Hb, Plate, WBC N
- Eosinophils 0.54 $X10^9/l$ (0.02-0.5)
- Biochemistry N
- CRP 8.3 mg/l (<5.0)
- Mycoplasma, EBV, CMV, Toxo, Parvovirus serology –ve
- C Burnetii serology -ve
- HIV 1/2 and HTLV1/2 serology –ve
- Herpes virus 7 -ve
- Hepatitis serology –ve
- Syphilis serology –ve
- ANA, ENA, dsDNA –ve
- Complement levels N

What is the most likely diagnosis?

1. Pustular psoriasis
2. Erythema multiforme
3. Acute generalised exanthematous pustulosis (AGEP)
4. Pityriasis lichenoides et varioliformis acuta (PLEVA)
5. Generalised herpes simplex infection

What is the most likely diagnosis?

1. Pustular psoriasis
2. Erythema multiforme
3. Acute generalised exanthematous pustulosis (AGEP) **TRUE**
4. Pityriasis lichenoides et varioliformis acuta (PLEVA)
5. Generalised herpes simplex infection

What is the most likely diagnosis now?

1. Subacute cutaneous lupus erythematosus
2. Erythema multiforme
3. Allergic contact eczema
4. Overlap between AGEP and DRESS syndrome
5. Pemphigus foliaceous

What is the most likely diagnosis now?

1. Subacute cutaneous lupus erythematosus
2. Erythema multiforme
3. Allergic contact eczema
4. Overlap between AGEP and DRESS syndrome **TRUE**
5. Pemphigus foliaceous

What would be the most appropriate systemic treatment?

1. Antihistamines
2. Dapsone
3. High dose IV Immunoglobulin
4. Mycophenolate
5. Prednisolone +/- Ciclosporin

What would be the most appropriate systemic treatment?

1. Antihistamines
2. Dapsone
3. High dose IV Immunoglobulin
4. Mycophenolate
5. Prednisolone +/- Ciclosporin TRUE

Severe Cutaneous Adverse Reactions (SCARs)

AGEP	1-11 days
SJS	4-28 days
DRESS	2-6 weeks

Drugs most commonly implicated - AGEP

- Amoxicillin
- Quinolones
- Sulfonamides
- Terbinafine
- Hydroxychloroquine
- Diltiazem

Key cells: CD8+ cytotoxic T cells and neutrophils
Key molecules: GM-CSF, IL-8, 17 and 22

Duong TA et al. Lancet 2017; 390:1996

DRESS Syndrome - Drug Reaction with Eosinophilia and Systemic Symptoms

- Fever > 38^{o}C
- Skin
  - Maculo-papular rash, erythroderma, facial or extremity oedema, purpura, pustules, focal mucous-membrane involvement
- Systemic Symptoms
  - Eosinophilia >700 cells per µL, atypical lymphocytes, elevated transaminase concentration, impaired renal function, herpesvirus family reactivation (HHV6, HHV7, EBV, CMV), parvovirus B19 reactivation

Drugs most commonly implicated - DRESS

- Carbamazepine
- Phenytoin
- Lamotrigine
- Allopurinol
- Sulfonamides
- Vancomycin
- Minocycline
- Amoxicillin

Key cells: CD8+ cytotoxic T cells, Th2 T cells and eosinophils
Key molecules: Eotaxin, IL-4, 5, 13, IFNγ and TNFα

Management of AGEP and DRESS

- Drug withdrawal
- Topical and systemic corticosteroids
- Supportive care
- Identification of culprit drug

Classification of SJS/TEN

- EMM
  - Mucous membrane involvement and cutaneous blistering with epidermal detachment of < 10% BSA.
- SJS
  - epidermal detachment < 10% BSA +
    widespread purpuric macules or flat atypical targets
- Overlap SJS–TEN
  - detachment of 10– 30% BSA +
    widespread purpuric macules or flat atypical targets
- TEN with spots
  - detachment > 30% BSA +
    widespread purpuric macules or flat atypical targets
- TEN without spots
  - detachment > 30% BSA and loss of large epidermal sheets without purpuric macules or target lesions

Drugs most commonly implicated - TEN

- Carbamazepine
- Phenytoin
- Lamotrigine
- Allopurinol
- Nevirapine
- NSAID*
- Sulfonamides
- Sulfasalazine

Key cells: CD8+ cytotoxic T cells and NK cells
Key molecules: Granulysin, perforin-granzyme B, Fas-Fas ligand and TNFα

GUIDELINES

BJD
British Journal of Dermatology

U.K. guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults 2016

- There is no conclusive evidence to demonstrate the benefit of any one intervention over conservative management

Br J Dermatol 2016;174:1194–1227

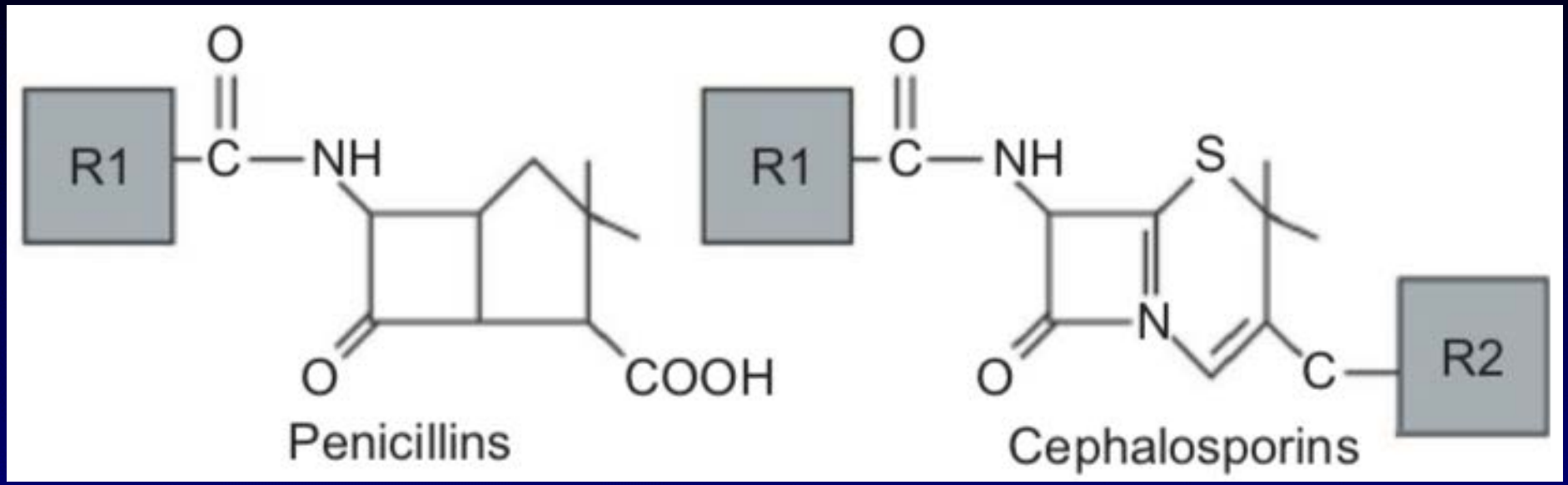
- ? High dose IVIg
- ? Ciclosporin
- ? Anti-TNFα biologics
- ?G-CSF

HLA associated Drug Reactions

Drug	HLA	Phenotype	Population	Screening
Abacavir	HLA-B*57:01	Hypersensitivity syndrome (HSS)	All	Avoid in HLA-B*57:01 +ve patients
Carbamazepine	HLA-B*15:02	SJS/TEN/ DRESS	Han Chinese, Thai, Malaysian, Indian	Avoid in HLA-B*15:02 +ve patients Screen at risk populations
Carbamazepine	HLA-A*31:01	HSS/DRESS/ SJS/TEN	Han Chinese, Japanese, Korean, Caucasian	Avoid in HLA-A*31:01 +ve patients
Allopurinol	HLA-B*58.01	HSS/DRESS/ SJS/TEN	Han Chinese, Thai, Korean, Japanese, Korean, European	No guideline
Phenytoin	HLA-B*15:02	SJS/TEN	Han Chinese, Thai	No guideline

Adler NR et al. Br J Dermatol 2017;177:1234, Duong TA et al. Lancet 2017; 390:1996,
Fan W-L et al. J Immunol Res 2017, in press

Drug Cross Reactivity
Penicillins and Cephalosporins



- Approx 20% between aminopenicillins (ampicillin, amoxycillin and bacampicillin) and aminocephalosporins (cephalexin and cefaclor)
- Low rate of cross reactivity between penicillin and nonaminocephalosporins (cefuroxime and ceftriaxone) and third- and fourth-generation cephalosporins

Adler NR et al. Br J Dermatol 2017;177:1234

Drug Cross Reactivity

- **Anticonvulsants**
  - **Cross reactivity between the aromatic anticonvulsants carbamazepine, oxcarbazepine, lamotrigine, phenytoin and phenobarbital**
  - **SAFE: valproate, gabapentin, pregabalin and levetiracetam**

- **Carbapenams and Penicillin**
  - **<1% cross reactivity between delayed hypersensitivity reaction to penicillin and carbapenams**

Adler NR et al. Br J Dermatol 2017;177:1234

Identifying Drug Causality

- Patch testing
  - Safe, 6/62 after SCAR
  - Highest sensitivity for abacavir (87%), anticonvulsants and beta-lactam antibiotics (44%)
  - Sensitivity 18% AGEP, 31.6-58% DRESS and lowest for SJS/TEN (20%-24%)
- Intradermal testing
  - Mainly for beta-lactam antibiotics
- In vitro tests
  - Lymphocyte stimulation tests
  - +/- IFNγ and IL-4 assays
  - Sensitivity >90%

Take Home Message

- THINK OF DRUGS
- ANNOTATE IN NOTES
- INFORM PATIENT AND GP in writing

Mr JN 15/05/80 Age 36

- 1982 Rheumatoid arthritis – GOS
  - Adverse reactions to Sulphasalazine and Methotrexate
- 1990 Crohn's disease
- Treated with Etanercept 50mg once weekly
- 1999 Arthrodesis of ankles
- Post-operatively DVT R calf
- Over the last 2 years recurrent ulcers on both lower legs
  - Not responding to ciclosporin 200mg daily for 4/12, pulsed methyl prednisolone 1gm X3, dapsone, minocycline

What is the most likely diagnosis of the cutaneous ulceration?

1. Cryoglobulinaema
2. Calciphylaxis
3. Bullous amyloid
4. Atypical mycobacterial infection
5. Pyoderma gangrenosum

What is the most likely diagnosis of the cutaneous ulceration?

1. Cryoglobulinaema
2. Calciphylaxis
3. Bullous amyloid
4. Atypical mycobacterial infection
5. Pyoderma gangrenosum TRUE

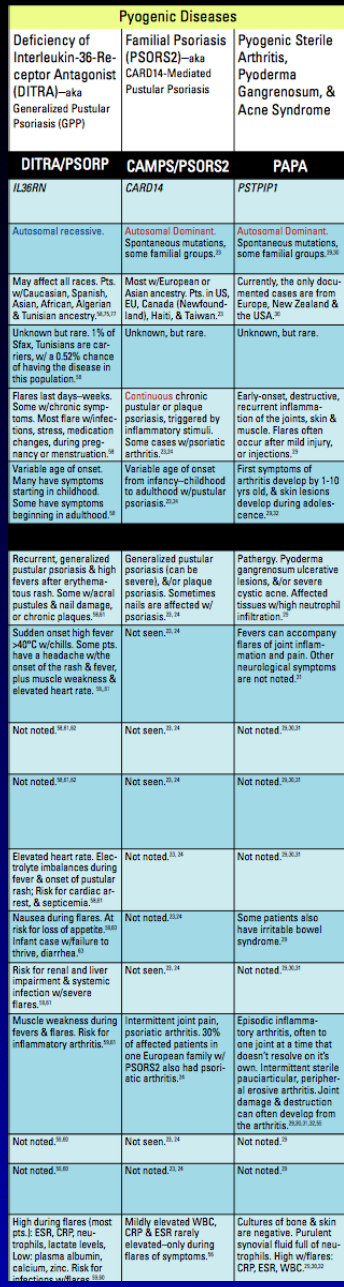
Diagnostic Criteria for Pyoderma Gangrenosum

- **Both Major criteria**
  - **Rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border**
  - **Other causes of cutaneous ulceration have been excluded**
- **+ 2 Minor criteria**
  - **History suggestive of pathergy or clinical finding of cribriform scarring**
  - **Systemic diseases associated with PG**
  - **Histopathologic findings (sterile dermal neutrophilia, ± mixed inflammation, ± lymphocytic vasculitis)**
  - **Treatment response (rapid response to systemic steroid treatment)**

Su WPD et al. Int J Dermatol 2004;43:790

AIDs including Pyoderma Gangrenosum

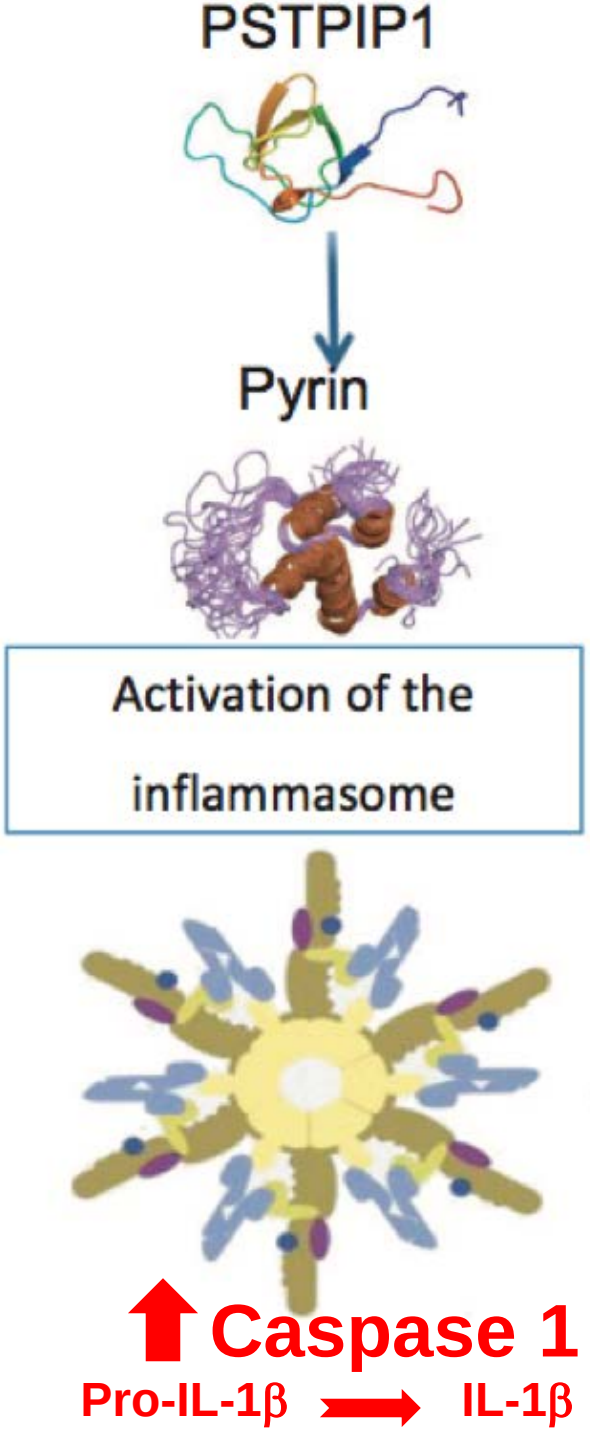
- PASH – PG, acne and suppurative hidradenitis
- PAPA – PG, acne and pyogenic arthritis
- PAPASH – PG, pyogenic arthritis, acne and suppurative hidradenitis
- PAC – PG, acne and ulcerative colitis
- PASS – PG, acne and seronegative spondylarthritis (Ank Spond)
- SAPHO – Synovitis, acne, pustulosis, hyperostosis and osteitis



Pyogenic Diseases		
Deficiency of Interleukin-36-Receptor Antagonist (DITRA)–aka Generalized Pustular Psoriasis (GPP)	Familial Psoriasis (PSORS2)–aka CARD14-Mediated Pustular Psoriasis	Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, & Acne Syndrome
DITRA/PSORP	**CAMPS/PSORS2**	**PAPA**
IL36RN	*CARD14*	*PSTPIP1*
Autosomal recessive.	Autosomal Dominant. Spontaneous mutations, some familial groups.[23]	Autosomal Dominant. Spontaneous mutations, some familial groups.[29,30]
May affect all races. Pts. w/Caucasian, Spanish, Asian, African, Algerian & Tunisian ancestry.[56,75,77]	Most w/European or Asian ancestry. Pts. in US, EU, Canada (Newfoundland), Haiti, & Taiwan.[23]	Currently, the only documented cases are from Europe, New Zealand & the USA.[30]
Unknown but rare. 1% of Sfax, Tunisians are carriers, w/ a 0.52% chance of having the disease in this population.[58]	Unknown, but rare.	Unknown, but rare.
Flares last days–weeks. Some w/chronic symptoms. Most flare w/infections, stress, medication changes, during pregnancy or menstruation.[58]	Continuous chronic pustular or plaque psoriasis, triggered by inflammatory stimuli. Some cases w/psoriatic arthritis.[23,24]	Early-onset, destructive, recurrent inflammation of the joints, skin & muscle. Flares often occur after mild injury, or injections.[29]
Variable age of onset. Many have symptoms starting in childhood. Some have symptoms beginning in adulthood.[58]	Variable age of onset from infancy–childhood to adulthood w/pustular psoriasis.[23,24]	First symptoms of arthritis develop by 1-10 yrs old, & skin lesions develop during adolescence.[29,30]
Recurrent, generalized pustular psoriasis & high fevers after erythematous rash. Some w/acral pustules & nail damage, or chronic plaques.[56,61]	Generalized pustular psoriasis (can be severe), &/or plaque psoriasis. Sometimes nails are affected w/ psoriasis.[23, 24]	Pathergy. Pyoderma gangrenosum ulcerative lesions, &/or severe cystic acne. Affected tissues w/high neutrophil infiltration.[29]
Sudden onset high fever >40°C w/chills. Some pts. have a headache w/the onset of the rash & fever, plus muscle weakness & elevated heart rate.[56,61]	Not seen.[23, 24]	Fevers can accompany flares of joint inflammation and pain. Other neurological symptoms are not noted.[27]
Not noted.[56,61,62]	Not seen.[23, 24]	Not noted.[29,30,31]
Not noted.[56,61,62]	Not seen.[23, 24]	Not noted.[29,30,31]
Elevated heart rate. Electrolyte imbalances during fever & onset of pustular rash; Risk for cardiac arrest, & septicemia.[56,61]	Not noted.[23, 24]	Not noted.[29,30,31]
Nausea during flares. At risk for loss of appetite.[59,60] Infant case w/failure to thrive, diarrhea.[63]	Not noted.[23,24]	Some patients also have irritable bowel syndrome.[29]
Risk for renal and liver impairment & systemic infection w/severe flares.[56,61]	Not seen.[23, 24]	Not noted.[29,30,31]
Muscle weakness during fevers & flares. Risk for inflammatory arthritis.[59,61]	Intermittent joint pain, psoriatic arthritis. 30% of affected patients in one European family w/ PSORS2 also had psoriatic arthritis.[24]	Episodic inflammatory arthritis, often to one joint at a time that doesn't resolve on it's own. Intermittent sterile pauciarticular, peripheral erosive arthritis. Joint damage & destruction can often develop from the arthritis.[29,30,31,32,59]
Not noted.[56,60]	Not seen.[23, 24]	Not noted.[29]
Not noted.[56,60]	Not noted.[23, 24]	Not noted.[29]
High during flares (most pts.): ESR, CRP, neutrophils, lactate levels, Low: plasma albumin, calcium, zinc. Risk for infections w/flares.[58,60]	Mildly elevated WBC, CRP & ESR rarely elevated–only during flares of symptoms.[58]	Cultures of bone & skin are negative. Purulent synovial fluid full of neutrophils. High w/flares: CRP, ESR, WBC.[29,30,32]

PSTIP1 mutation in PASH and PAPA

- PSTP1 encodes proline-serine-threonine phosphatase-interacting protein 1 which is a cytoskeleton-associated adaptor protein of the inflammasome
- PSTIP1 mutations cause inhibition of the anti-inflammatory effect of pyrin, upregulation of caspase-1, activation of IL-1, producing a neutrophil-mediated autoinflammatory response
- Other mutations in NOD, IL1RN and NLRP3 genes in PASH



Calderon_Castrast X et al. Br J Dermatol 2016;175:194
Marzano AV et al. Medicine 2014;93:e187

Additional Mutations causing PASH and other PG syndromes

- **PASH - Nicastrin mutation- type I transmembrane glycoprotein that is an integral component of the multimeric gamma-secretase complex. The encoded protein cleaves integral membrane proteins, including Notch receptors**

Duchatelet S et al. Br J Dermatol 2015;173:610

- **PSTPIP1 mutation causing hyperzincaemia and hypercalprotectinaema (Hz/Hc)**
  - **Pyoderma gangrenosum**
  - **Hepatosplenomegaly**
  - **Failure to thrive**
  - **Arthritis**
  - **Pancytopaenias**

Holzinger D et al. J Allergy Clin Immunol 2015;136:1337

Inflammasomes
Multimeric complexes formed in response to physiological and pathogenic stimuli

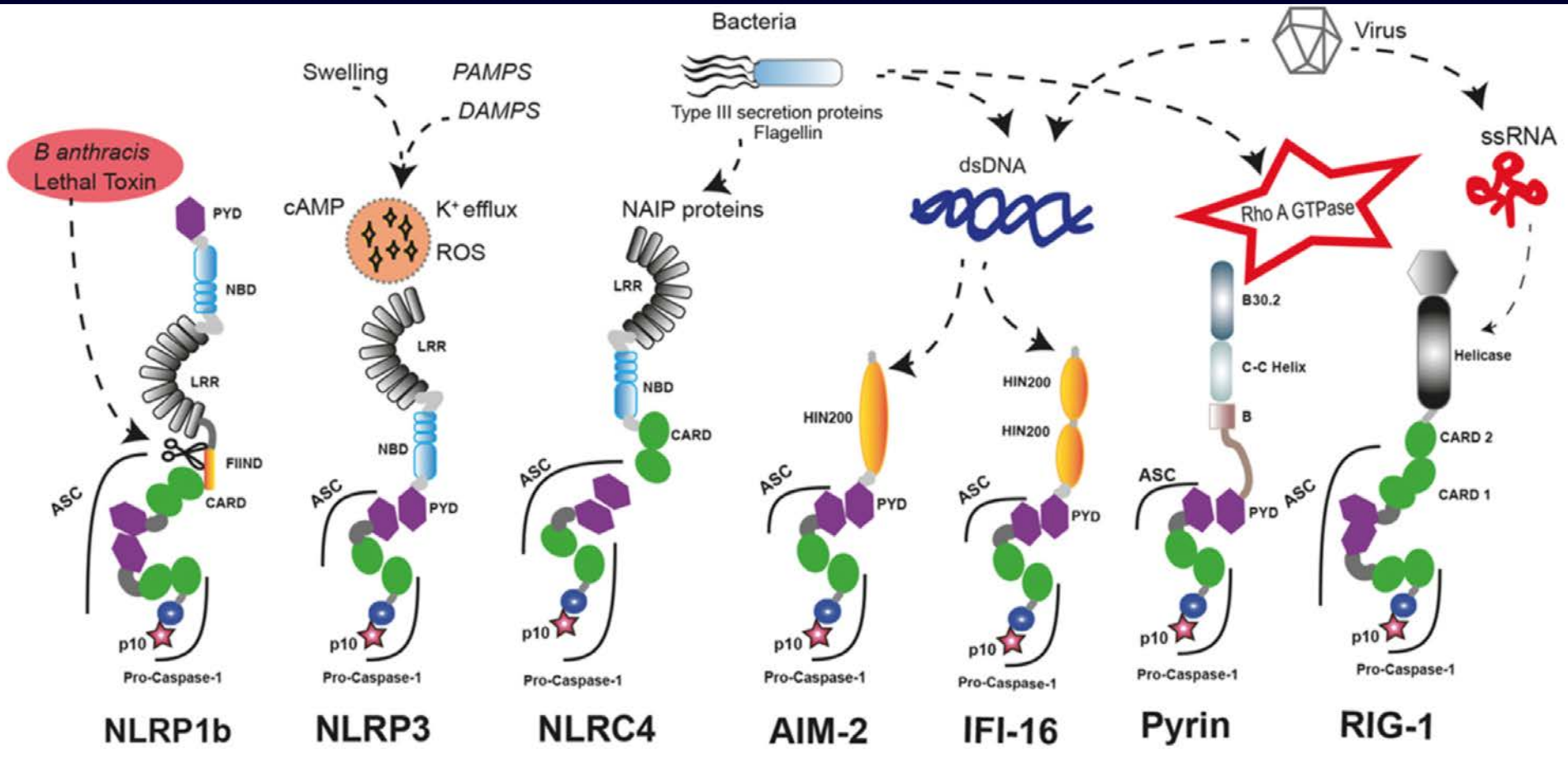
Cytosolic Inflammasome Sensors

ASC; apoptosis-associated speck-like protein containing a caspase activation and recruitment domain

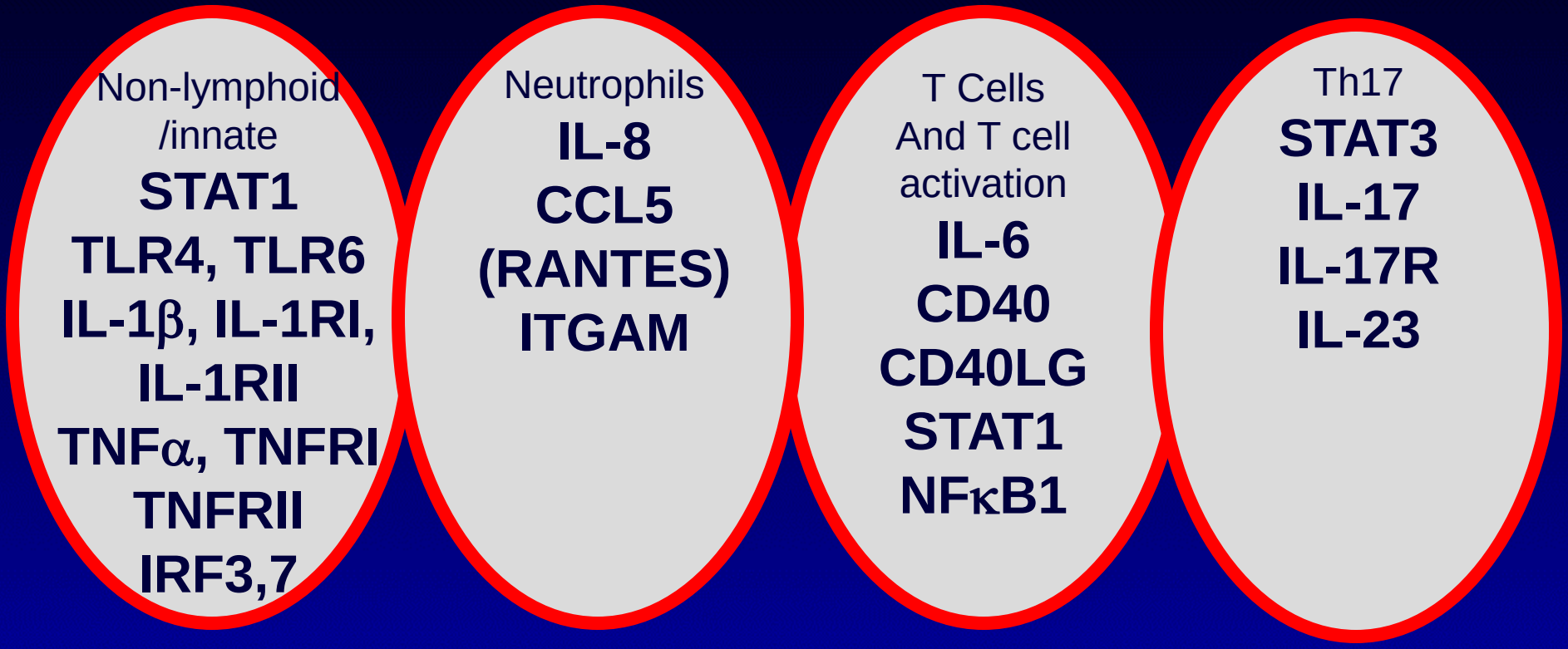
Adaptor Molecule ASC ➡ nucleated

Recruits caspase-1 which is cleaved to produce the active subunits p10 and p20. These active proteolytically process cytokines IL-1β and IL-18, and induce a specific form of inflammatory cell death, pyroptosis

Inflammasome Activators and Sensors

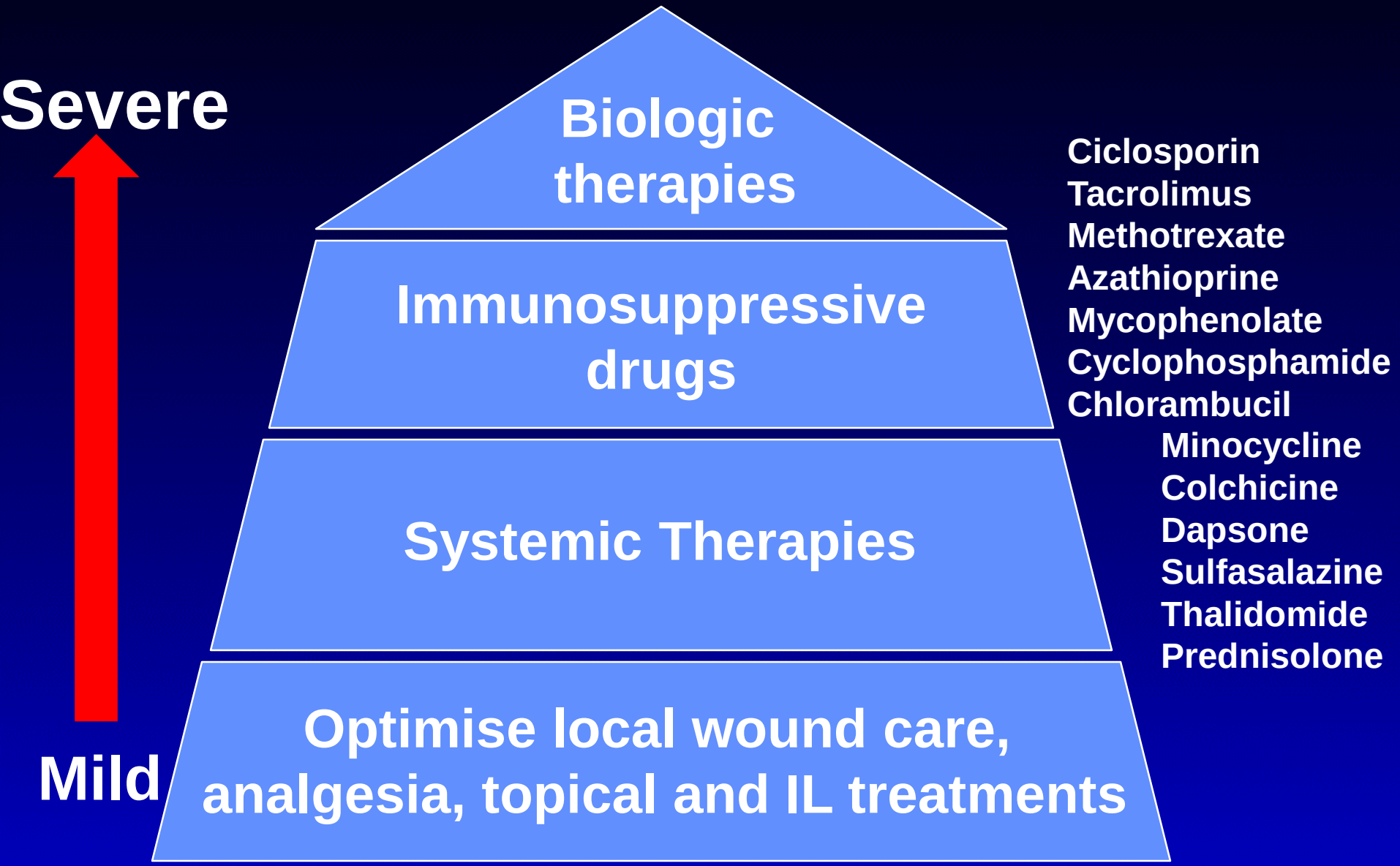


Dysregulation of Cytokine and Gene Expression in PG



Lesional PG skin. Marzano AV. Clin Exp Immunol 2014;178:48
Lesional V Nonlesional PG skin. Ortega Loayna AG et al. Br J Dermatol 2017 in press
Guenova E et al. Arch Dermatol 2011;147:1203

Treatment of Pyoderma Gangrenosum



Which Biologic would be the most efficacious for this patient?

- Rituximab
- Infliximab
- Toficitinib
- Tocilizumab
- Alemtuzumab

Which Biologic would be the most efficacious for this patient?

- Rituximab Anti-CD20
- Infliximab TRUE
- Toficitinib JAK1-3 inhibitor
- Tocilizumab Anti-IL-6R
- Alemtuzumab Anti-CD52 (CD3+ and CD19+ lymphocytes)

Treatment of Pyoderma Gangrenosum

- NO national or international guidelines
- Poorly evidenced publications
- 2 Randomised controlled trials
  - Infliximab
  - STOP GAP trial

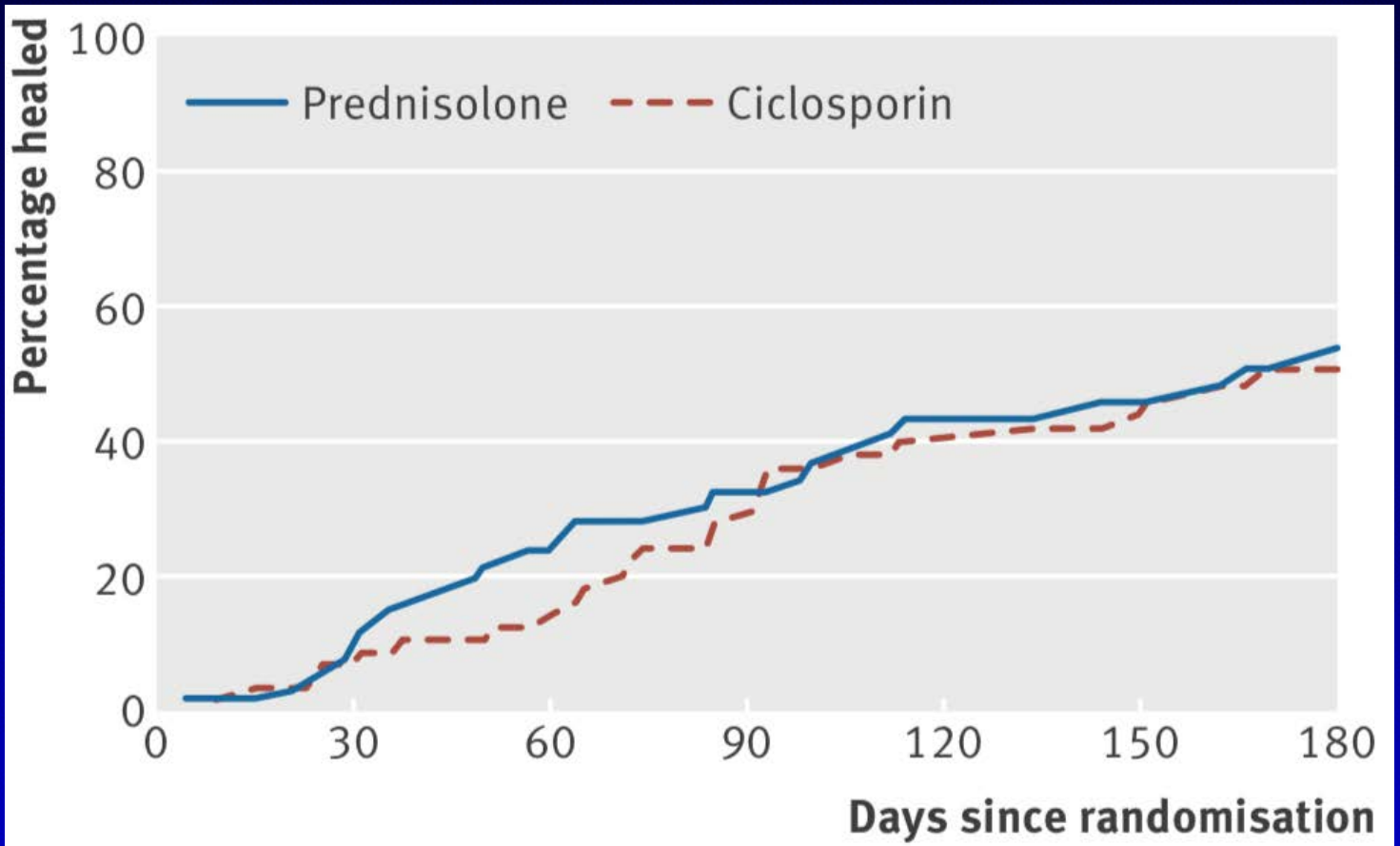
Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial

- **Randomised to placebo or infliximab 5mg/kg IV at week 0**
- **Assessed at week 2, if no improvement open treatment with infliximab 5mg/kg**
- **At Week 2; 46% improvement with Infliximab: 6% placebo**
- **At Week 6; 69% improvement with Infliximab**

Brooklyn TN et al. Gut 2006;55:505

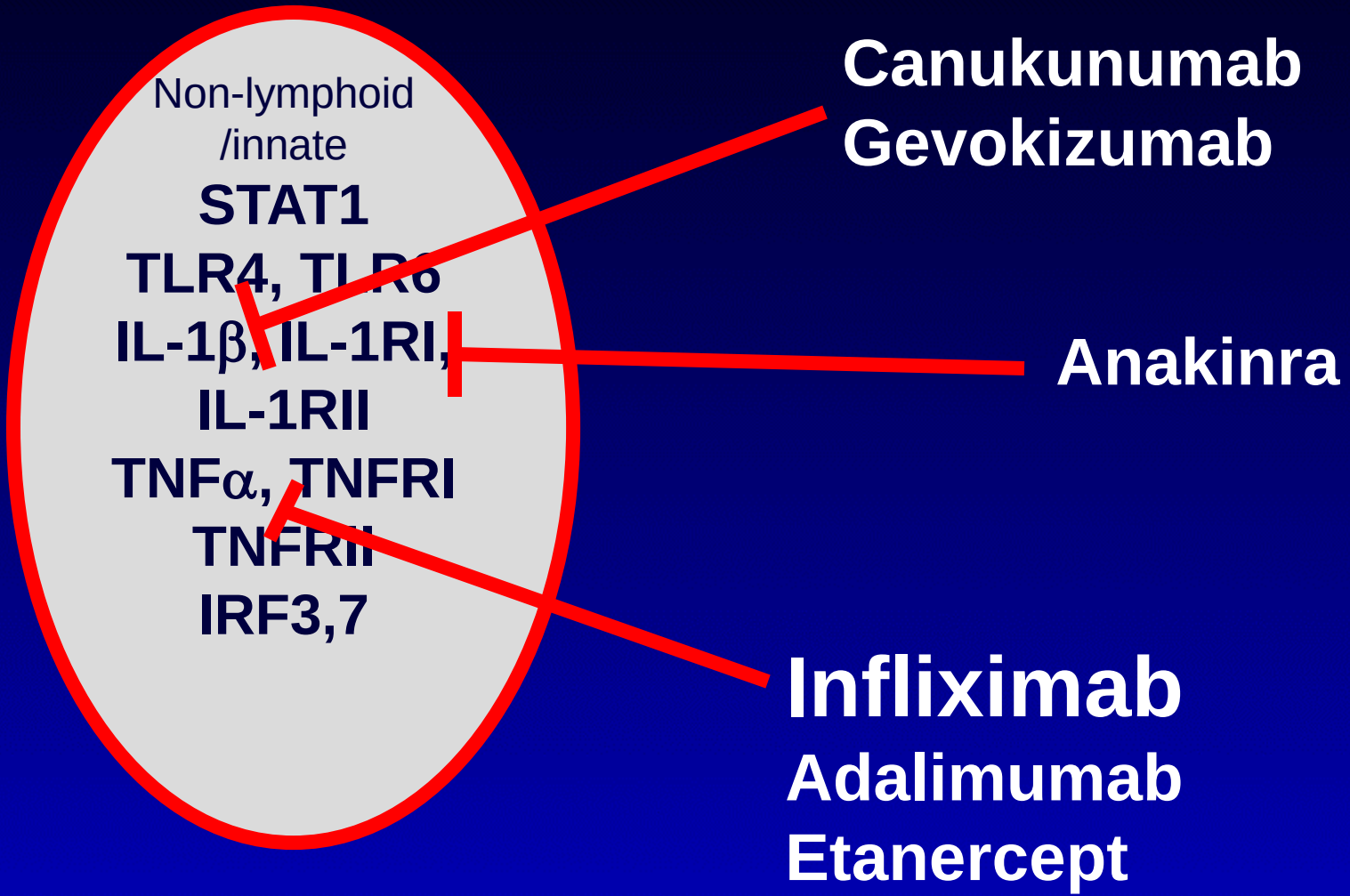
Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomised controlled trial

- **N=121 with PG**
- **Intervention: Prednisolone 0.75 mg/kg/day compared with ciclosporin 4 mg/kg/day, to a maximum dose of 75 and 400**

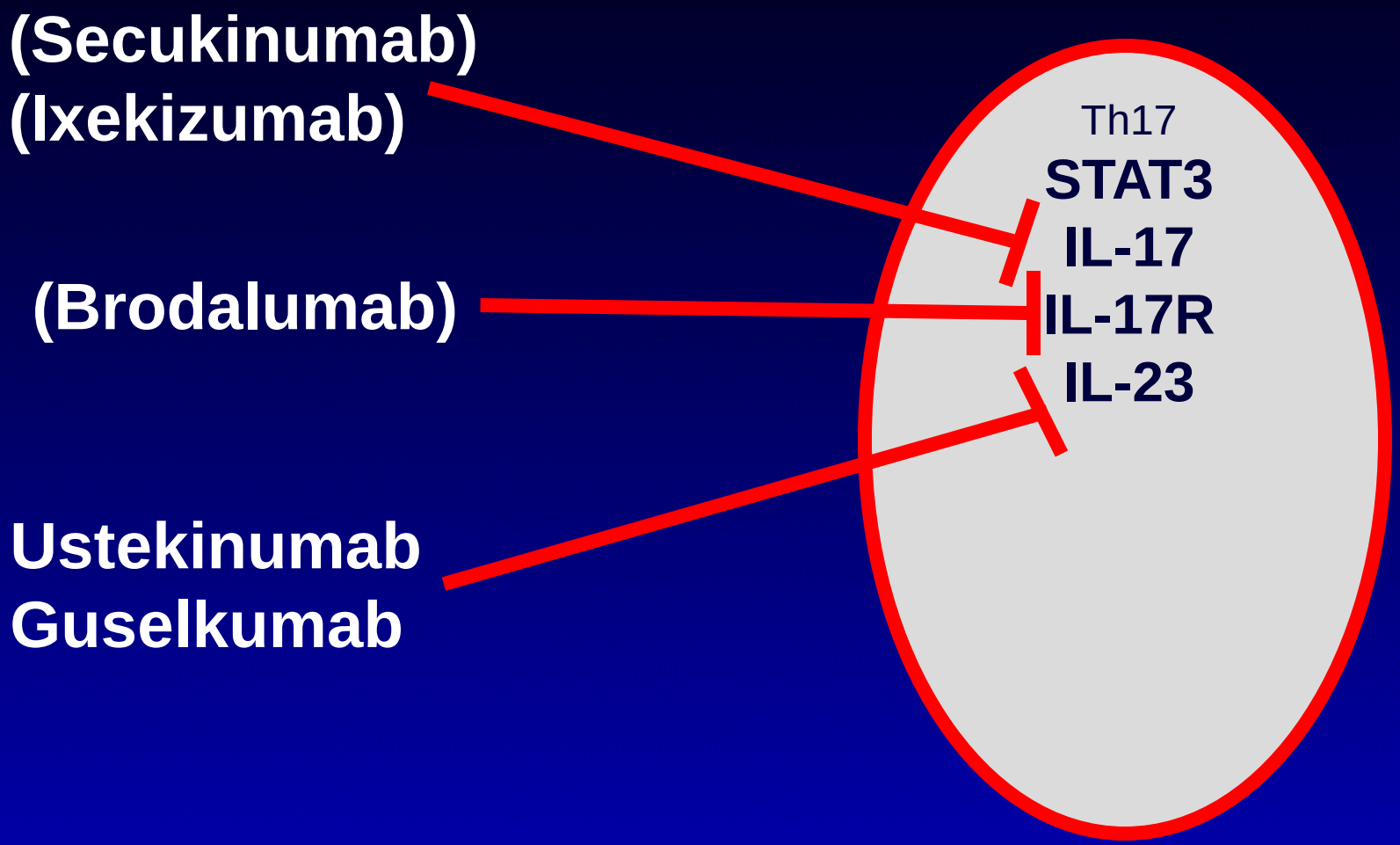


Ormerod AD et al. BMJ 2015; 350:1

Rationale of Biologic based upon Cytokine Dysregulation in PG



Rationale of Biologic based upon Cytokine Dysregulation in PG



Take Home Message

- THINK OF MEDICAL CAUSES FOR LEG ULCERS