



# *Generalized pustular psoriasis for the rheumatologist*

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# *Aims*

- u **To learn how to diagnose generalized pustular psoriasis and how it may present as an autoinflammatory syndrome**
- u **Develop an approach to therapy of GPP**

# *Faculty Disclosure*

- Faculty: Jan Peter Dutz
- Relationships with financial sponsors
  - » Clinical trials
    - Astra Zeneca, GSK
  - » Speaker's Bureau/Honoraria
    - Astra Zeneca, AbbVie, Amgen, Bausch, Bristol Myers Squibb, Celltrion, Galderma, Leo, Johnson & Johnson, Novartis, Pfizer, Sanofi

# *Disclosure of Financial Support*

- **No external support**

## *59 F with fever and rash*

- 2 week history of fever and rash
- Elevated ferritin and chest pain – pericarditis? Rx Naproxen
  - Ferritin >16,000, ANA, RF –ve
  - WBC 23.4: N 15.3, L 3.9 ; Eo N; Plt 68
  - CRP 136
  - ALP 319; renal function normal

## *59 F with fever and rash*

### □ Past history

- T2DM, hypertension
- Febrile episode 2013 – 2 weeks with rash treated empirically with prednisone
- Still's disease was considered

### □ Medications

- Colchicine, amlodipine, linagliptin, furosemide

# *59 F with fever and rash*

## □ Examination

- Febrile (38.7)
- No arthritis
- No localizing findings



- **Erythroderma**
  - Drug Rx?
  - Lymphoma?
  - Dermatitis?
  - Psoriasis?
  - Pityriasis rubra pilaris?

# *59 F with fever and rash*

## □ **Course**

- **Cultures (bacterial, viral) negative**
- **Liver BX**
  - » **Patchy portal inflammation**
- **Skin BX**
  - » **Psoriasiform spongiotic dermatitis**
- **Defervescence**
- **Discharged after 10 days – hyperinflammatory state NYD**

## *59 F with fever and rash*

- **Course**

- **Readmitted – 5 days later with recurrent fevers**



## *59 F with fever and rash*

### □ **Course**

- Pustules noted
- **DX Generalized pustular psoriasis (GPP)**
  
- **Treated with infliximab with improvement**

## *59 F with fever and rash*

### □ **Course**

- **Ongoing itch, rash, and elevated inflammatory markers x 5 months**
- **Anakinra – no improvement**
- **Phototherapy + MTX - no improvement**

# 59 F with fever and rash

## □ Course

- Genetic testing

  - » IL36Ra, IL1, AP1S3, MPO normal

- Cytokine testing

  - » IL18 10X; IP10; IFN $\gamma$ ; IL-5; IL6

- IV spesolimab (anti IL36R Ab) = resolution

## *59 F with fever and rash*

### □ **Course**

- **Readmitted 6 mo later with RUQ pain, fever, rash**
- **ERCP – no stones**
  
- **IV spesolimab - resolution**

*Leo Franz Caspar von Zumbusch*  
(1874-1940)



# Leo Ritter von Zumbusch (1874-1940)

- 2 siblings (M + F)
- Psoriasis
- Recurrent fevers erythema and pustulosis

Zumbusch LR. Psoriasis und pustulöses Exanthem. *Archiv für Dermatol Syph.* 1910;99:335-46.

Aus der k. k. Universitätsklinik für Dermatologie und Syphilidologie zu Wien [Vorstand Prof. Dr. G. Riehl].

## Psoriasis und pustulöses Exanthem.

Von

Dr. Leo Ritter von Zumbusch.

Im folgenden soll eine Beobachtung an zwei Kranken wiedergegeben werden, die aus verschiedenen Gründen nicht uninteressant ist. Die beiden Kranken, Bruder und Schwester, standen an der Klinik in Behandlung, ein Fall kam zur Sektion. Zunächst seien die Krankengeschichten wiedergegeben und zwar, um die Sache zu beleuchten, in voller Ausführlichkeit:

I. Josef N., 24 J., Tagelöhner aus Floridsdorf bei Wien.

Anamnese vom 20. August 1888. Der sonst gesunde Patient steht seit längerer Zeit mit Psoriasis an der Klinik in Behandlung. Vor 2-3 Monaten lag Patient an der Klinik mit einem toxischen Ekzem, welches er sich durch Auflegen einer Salbe gegen Psoriasis sogenannt haben will. Dasselbe soll in Form hirsekorn- bis stecknadelkopfgroßer gruppiertes Pustelchen aufgetreten sein, Patient wurde damals geheilt entlassen. (Die Krankheitsgeschichte dieses ersten Spitalsaufenthaltes ist nicht auffindbar.)

Status praesens: An beiden Unterschenkeln handtellergroße plaquesartige psoriatische Stellen, in deren Umgebung die Haut stark gereizt und entzündet ist. An beiden Vorderarmen und am unteren Drittel beider Oberarme die Haut stark gerötet, entzündlich geschwollen, namentlich an den Biegeseiten mit dicht nebeneinander stehenden, hirsekorn- bis stecknadelkopfgroßen Pustelchen besetzt. Sonst sieht, man am Körper zerstreut linsengroße, und größere Psoriasisfloreszenzen, ebensolche auch an den Ohren und im Bereich der behaarten Kopfhaut. Therapie: Umschläge mit Liq. Burowii.

22./VIII. Alle Bläschen verschwunden, die Haut ist noch rot und mäßig infiltriert.

29./VIII. Pat. wird mit Creolin salbe behandelt.

12./IX. Überall ist die Haut abgelaßt, schuppig, die Entzündungserscheinungen im Rückgang begriffen.

# *Pustular psoriasis*

- **Generalized pustular psoriasis (GPP)**
  - von Zumbusch type
- **Annular or circinate pustular psoriasis**
- **Exanthematous pustular psoriasis**
  - Post infectious or drug induced
  - Acute generalized exanthematous pustulosis (AGEP)
- **Localized pustular psoriasis (palmoplantar)**

# *GPP - Definitions*

- **2018 Japanese guidelines**
    - **Systemic symptoms**
    - **Extensive flushing with sterile pustules**
    - **Subcorneal neutrophilic pustules**
    - **Repeated recurrences**
- 4/4 Dx 2-3/4 Susp**

*Fujita H J Dermatol. 2018;45:1235*

# *Generalized pustular psoriasis*

- Prevalence of up to 150 per million
  - 7.46 per million in Japan
  - 1.76 per million in France
- Mean age of onset 30-60 YO
- Female predominance 1.5-2:1
- Associated with plaque psoriasis in 30-60%
- Pathophysiology different than psoriasis

# *GPP - Definitions*

## **2017 ERASPEN criteria - Europe**

- **Primary Lesion:** Presence of macroscopically visible, sterile pustules on an erythematous base (non-acral skin).
- **Course:** Relapsing (at least one previous episode) or persistent (>3 months).
- **Location:** Non-acral skin (GPP should not be diagnosed if pustulation is strictly restricted to the palms and soles, which is deemed palmoplantar pustulosis).
- **Context:** Can occur with or without accompanying psoriasis vulgaris.

# *GPP - Definitions*

- **2024 International Psoriasis Council**
  - **33 global GPP experts voted on 43 statements**
  - **2 Delphi rounds**

*Choon SE JAMA Dermatol. 2024;160(7):758*

# GPP - Definitions

- 2024 International Psoriasis Council
  - 33 global GPP experts voted on 43 statements
  - 2 Delphi rounds

Choon SE JAMA Dermatol. 2024;160(7):758

## Definition

GPP is a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules.

## Subclassifiers

1. It may manifest with or without systemic symptoms and signs.
2. It may or may not be associated with other types of psoriasis.
3. GPP can present as an acute form with widespread pustular eruption or a subacute variant with annular phenotype.
4. Laboratory abnormalities may or may not be present.

## Diagnostic Criteria

### Essential

Macroscopically visible sterile pustules on erythematous base and not restricted to the acral region or within psoriatic plaques

### Supporting

- Lakes of pus
- Painful skin
- Fatigue
- Fever
- History of recurring flares
- Positive personal or family history of psoriasis
- Elevated CRP
- Leukocytosis
- Neutrophilia
- Abnormal laboratory tests such as hypocalcemia, hypoproteinemia, hypoalbuminemia, abnormal liver or renal functions
- Biopsy confirmation with the presence of spongiform pustules of Kogoj
- Any positive genetic finding (namely *IL36RN* mutation, *MPO*, *API53*, *SERPINA*, *CARD14*)

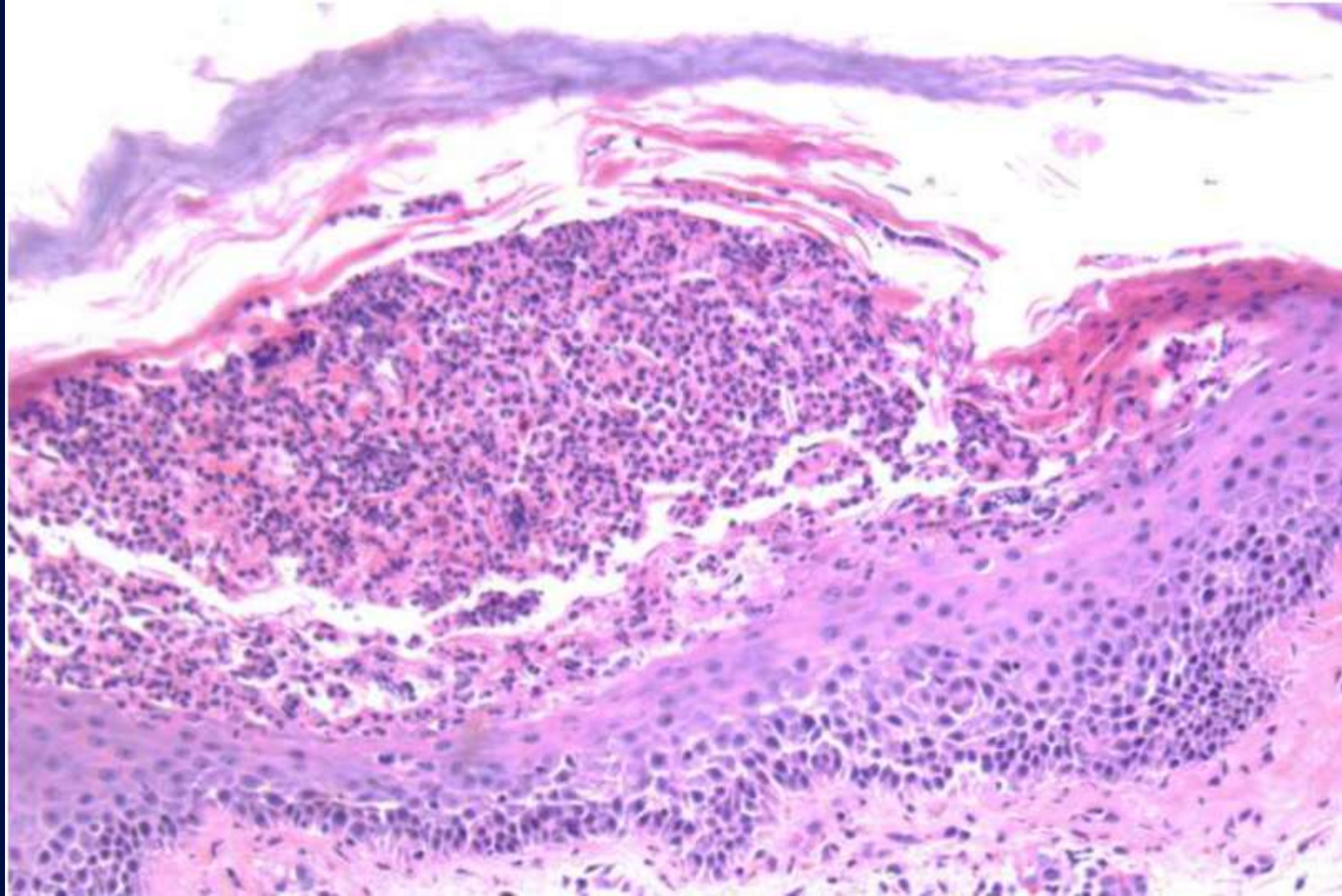
Abbreviation: CRP, C-reactive protein.



*Dermatology, Bologna 5<sup>th</sup> Ed 2025*

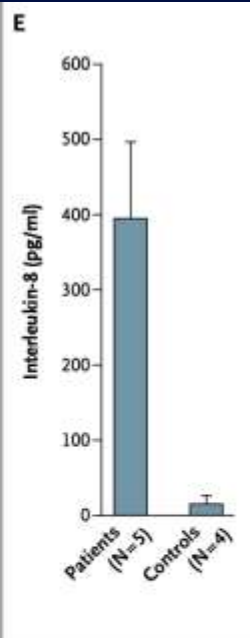
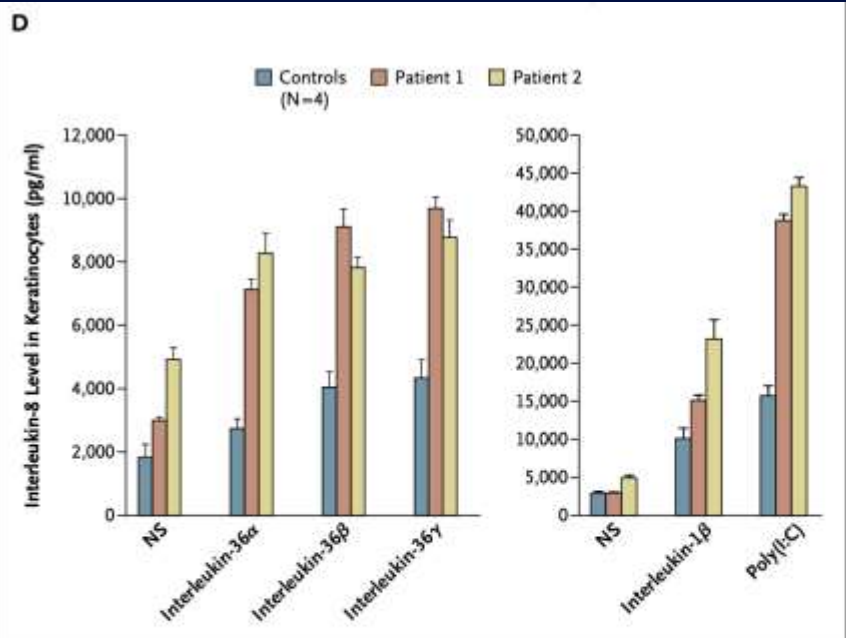


*Dermatology, Bologna 5<sup>th</sup> Ed 2025*

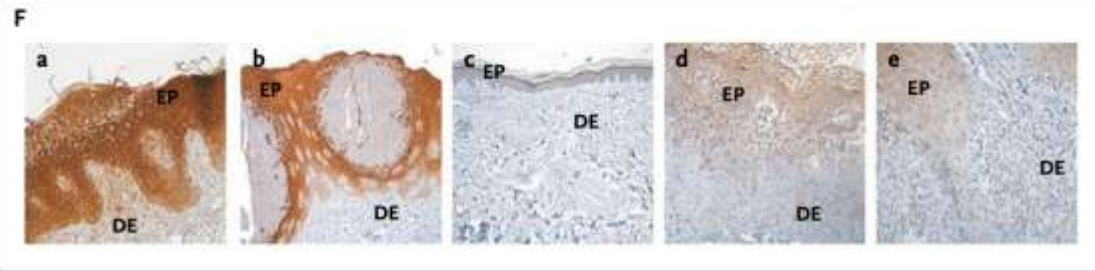


# *DITRA – Deficiency of interleukin 36 –Receptor antagonist*

- **9 multiplex Tunisian families studied**
- **AR recurrent pustular psoriasis**
- **Mutant interleukin 36Ra protein**
  - **Increased keratinocyte inflammation**
  - **Increased keratinocyte gamma expression**

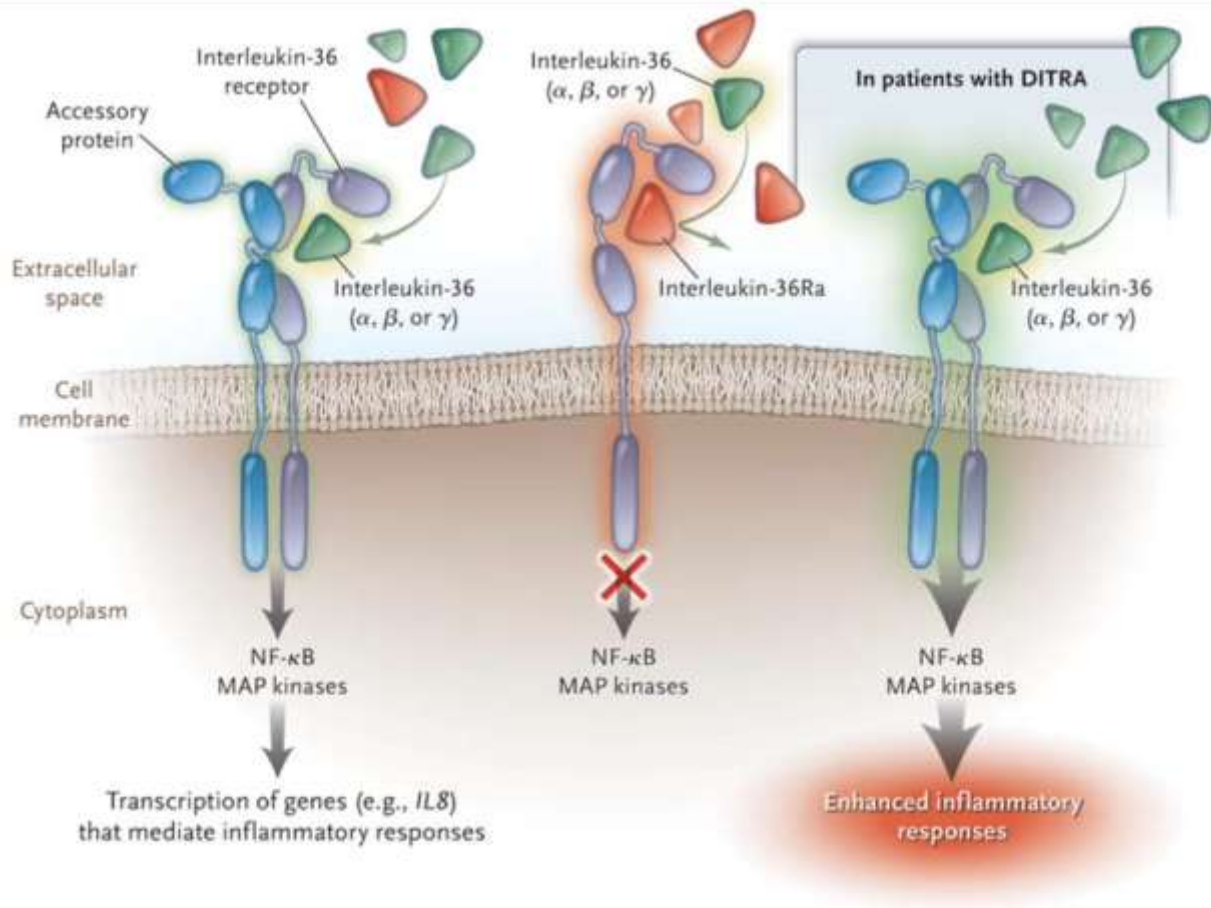


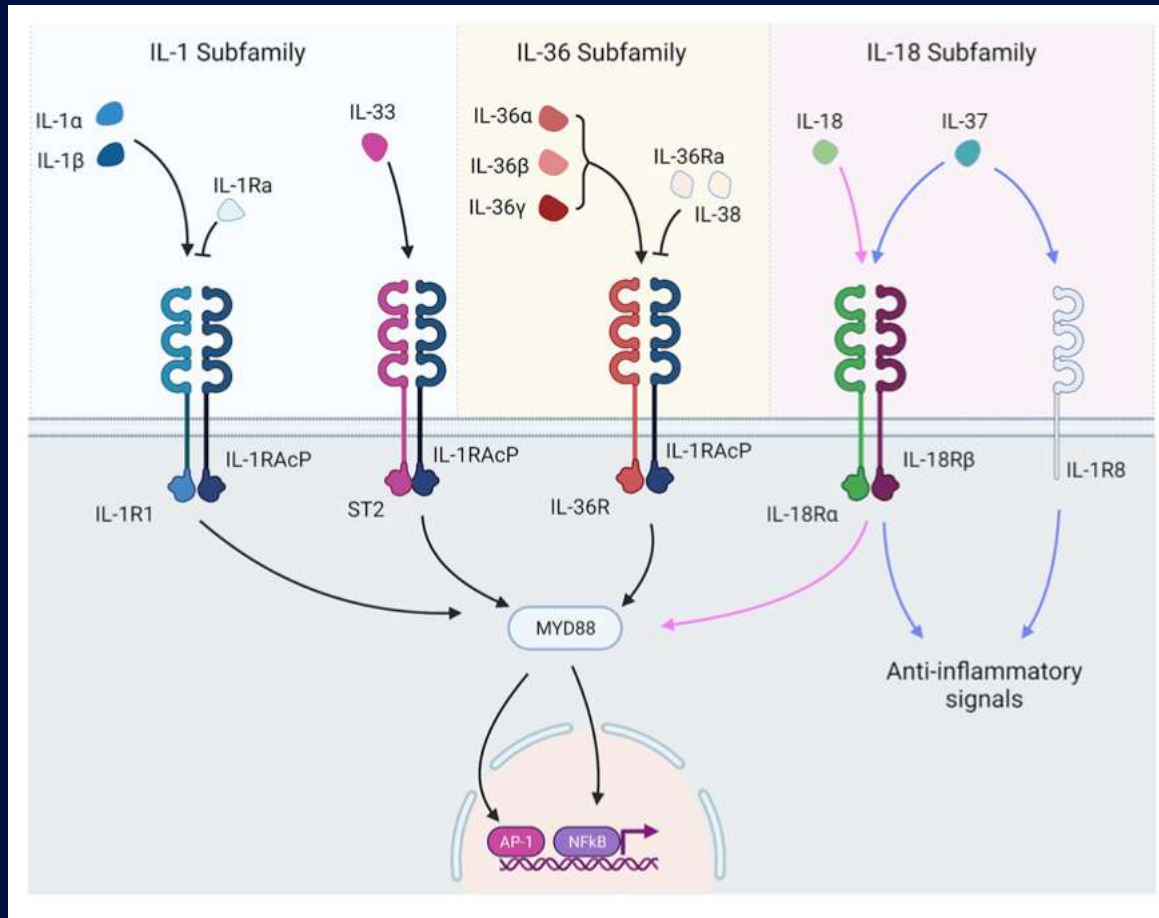
IL8 production is increased in keratinocytes and blood

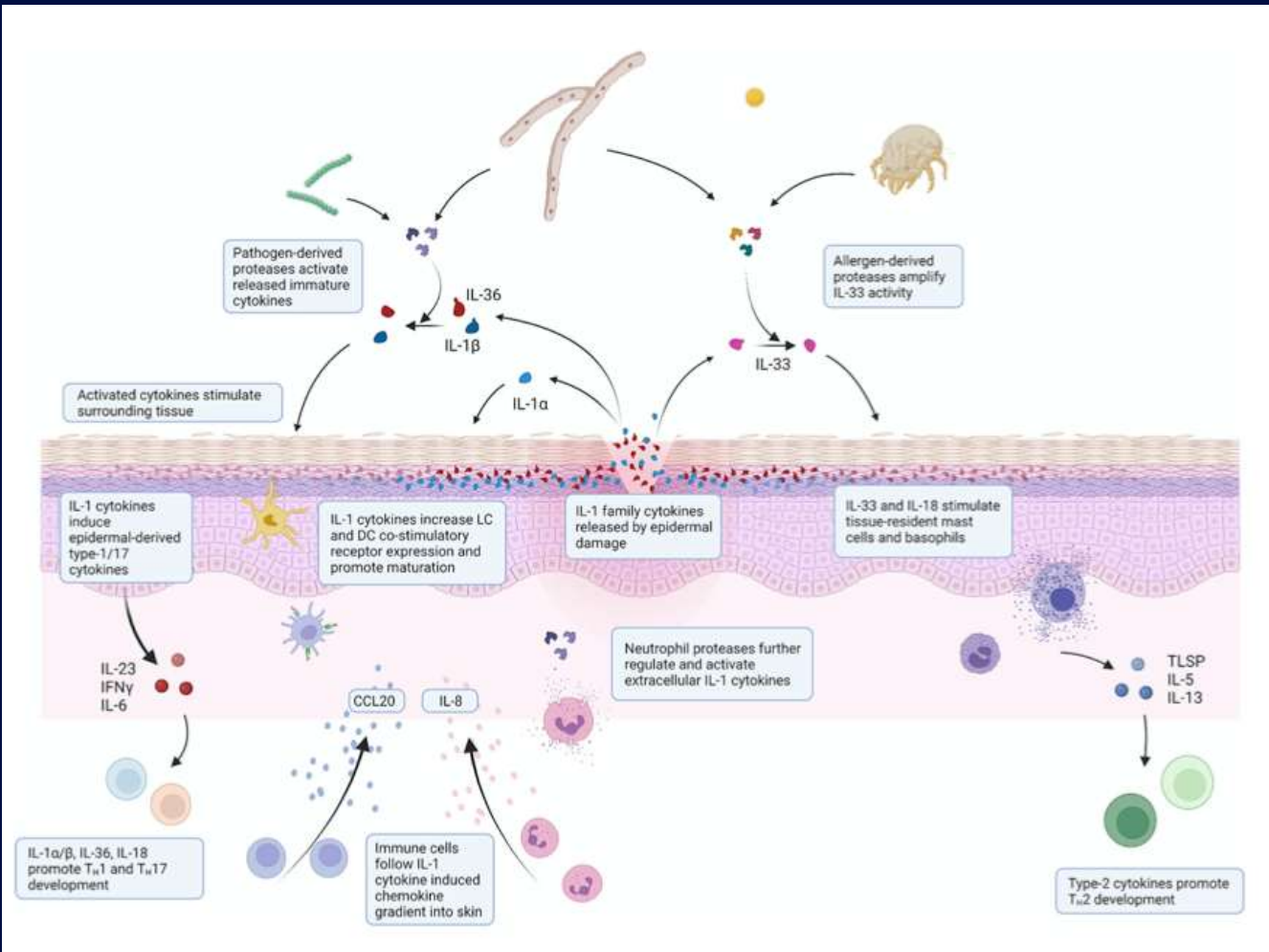


IL36gamma expression

Patients                      Normal                      Lichen pl                      TEN





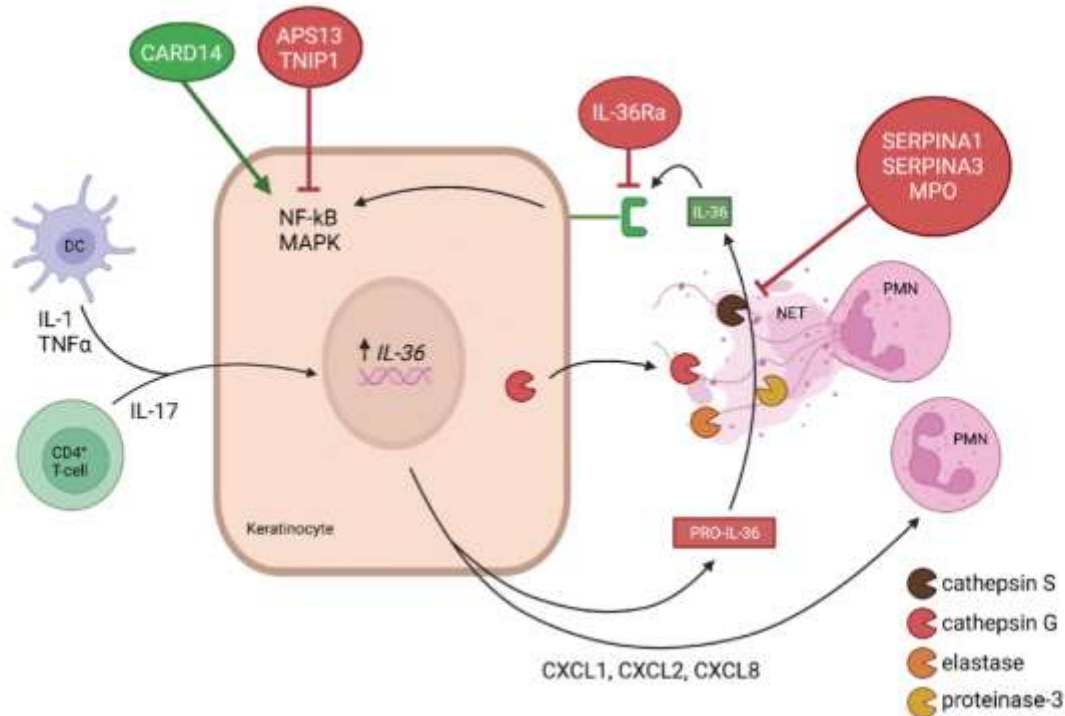


# Genetic mutations associated with GPP

Gene	Protein	Proposed Effect	Proposed GPP Mechanism	Associated Disorders	GPP	PPP	ACH	APP	PV
IL1RN	IL1-RN	LOF	Loss of IL-1 antagonism	DIRA					
IL36RN	IL36-Ra	LOF	Loss of IL-36 antagonism	DITRA	+	+	+		+
CARD14	CARD14	GOF	Enhanced NF-κB signalling	PRP	+	+			+
AP1S3	AP1S3	LOF	Enhanced NF-κB signalling		+	+	+		+
MPO	MPO	LOF	Enhanced neutrophil protease activity; Decreased neutrophil turnover		+	+		+	
SERPINA1	SERPINA1	LOF	Loss of protease inhibitor activity; Enhanced IL-36 activation		+				
SERPINA3	SERPINA3	LOF	Loss of protease inhibitor activity; Enhanced IL-36 activation		+				
TNIP1	TNFAIP3-interacting protein 1		Enhanced NF-κB signalling		+				

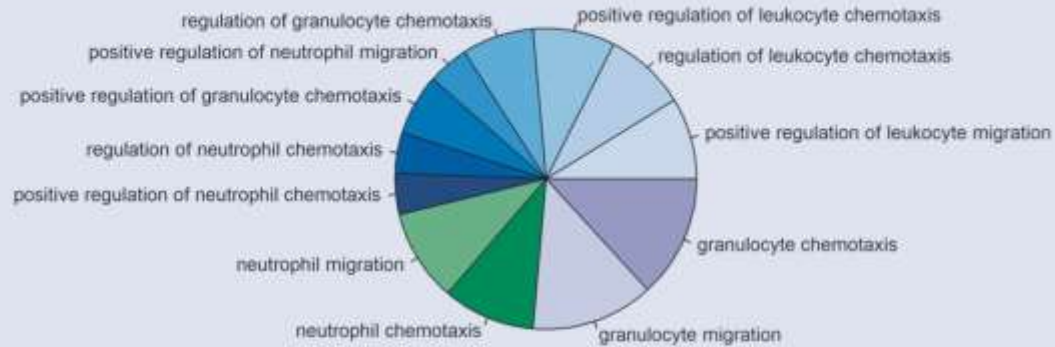
Abbreviations: ACH, acrodermatitis continua of Hallopeau; APP, annular pustular psoriasis; GPP, Generalized pustular psoriasis; PPP, palmoplantar pustular psoriasis; PRP, pityriasis rubra pilaris; PV, psoriasis vulgaris.

# Genetic mutations associated with GPP



Young, *Experimental Dermatology*. 2023;32:1194

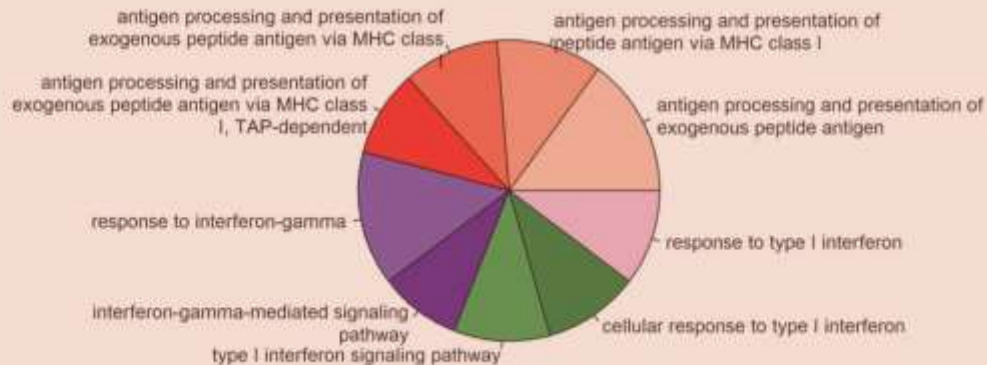
### Generalized Pustular Psoriasis



Autoinflammation  
Innate Immune System  
IL-1/IL-36

Autoimmune  
Adaptive Immune System  
IL-17/IL-23

### Psoriasis Vulgaris



# *Clinical manifestations*

- Rapidly erupting painful 2-3 mm papules and pustules
- Within areas of erythema
- May coalesce – lakes of pus
- Extend over hours to days
- Resolve with desquamation

# *Clinical manifestations*



*Romiti, Anais Brasileiros de Dermatologia (2022);97(1):63*

# *Clinical manifestations*



*Romiti, Anais Brasileiros de Dermatologia (2022);97(1):63*

# *Clinical manifestations*

- **Flares – last 2-8 weeks**
- **Look for evidence of psoriasis (30%)**
  - **Nail drop**
  - **Scalp**

# *GPP is a systemic illness*

- **Fever**
- **Systemic inflammatory response syndrome**
- **Arthritis**
- **0.5-1 flare per year**
- **Significant mortality rate**

# *GPP and the GI tract*

- ❑ **Gastrointestinal bleeding**
- ❑ **Neutrophilic cholangitis**
  - **Recurrent acute cholangitis**  
**Allez Journal of Hepatology 2000; 33: 16**
- ❑ **Cholestatic jaundice**
  - **Dramatic response to infliximab**  
**Chandran Australasian Journal of Dermatology (2010) 51, 29**

# *GPP Flare triggers*

- ❑ **True triggers are still unknown**
- ❑ **Patients without psoriasis may flare more often**
- ❑ **Corticosteroid withdrawal is commonly cited**
- ❑ **Infections, pregnancy, stress**

# *GPP is associated with increased mortality*

- **Meta-analysis of US and Sweden data**
- **All cause mortality**
  - **1.78 compared to psoriasis**
  - **2.92 compared to general population**

*Strober Dermatol Ther (Heidelb) (2026) 16:377*

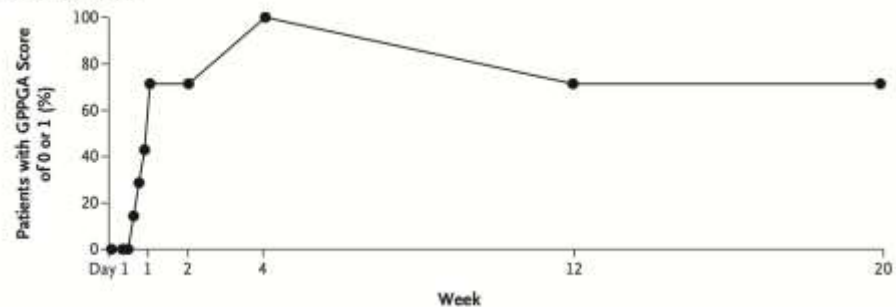
# Spesolimab – anti IL36R Ab

Bachelez NEJM 380; 10 981 (2019)

A Two Study Patients before and after Treatment with BI 655130



B GPPGA Score of 0 or 1



# Spesolimab – anti IL36R Ab

## EFFAYSIL1

Bachelez NEJ 2021;385:2431 (2021)

**Table 1.** Demographic and Clinical Characteristics of the Patients at Baseline.\*

Characteristic	Spesolimab (N=35)	Placebo (N=18)
Age — yr	43.2±12.1	42.6±8.4
Weight — kg	73.7±24.0	68.8±26.6
Female sex — no. (%)	21 (60)	15 (83)
Race — no. (%)†		
Asian	16 (46)	13 (72)
White	19 (54)	5 (28)
GPPGA total score — no. (%)‡		
3	28 (80)	15 (83)
4	7 (20)	3 (17)
GPPGA pustulation subscore — no. (%)§		
2	6 (17)	5 (28)
3	16 (46)	7 (39)
4	13 (37)	6 (33)
Median GPPASI total score (IQR)¶	27.4 (15.5–36.8)	20.9 (12.0–32.0)
IL36RN mutation — no. (%)		
Yes	5 (14)	2 (11)
No	24 (69)	12 (67)

**Table 2. Primary and Key Secondary Efficacy End Points.**

End Point	Spesolimab (N=35)	Placebo (N=18)
Primary end point: GPPGA pustulation subscore of 0 at wk 1		
Response — no. of patients (%)	19 (54)	1 (6)
Difference vs. placebo (95% CI) — percentage points	49 (21–67)	
P value*	<0.001	
Key secondary end point: GPPGA total score of 0 or 1 at wk 1		
Response — no. of patients (%)	15 (43)	2 (11)
Difference vs. placebo (95% CI) — percentage points	32 (2–53)	
P value*	0.02	

\* Shown are two-sided P values calculated by means of the Suissa–Shuster z-pooled test.

*Bachelez NEJ 2021;385:2431 (2021)*

# *Spesolimab and flare prevention*

- **Multicenter phase 2B trial across 20 countries**
- **Documented history of GPP (ERASPEN)**
- **History of 2 flares**
- **High dose: Medium dose: Low dose:PI**
- **SQ drug**
  - 300mg + 150mg q 12W
  - 600mg + 300mg q 12W
  - 600mg + 300mg q 4 W

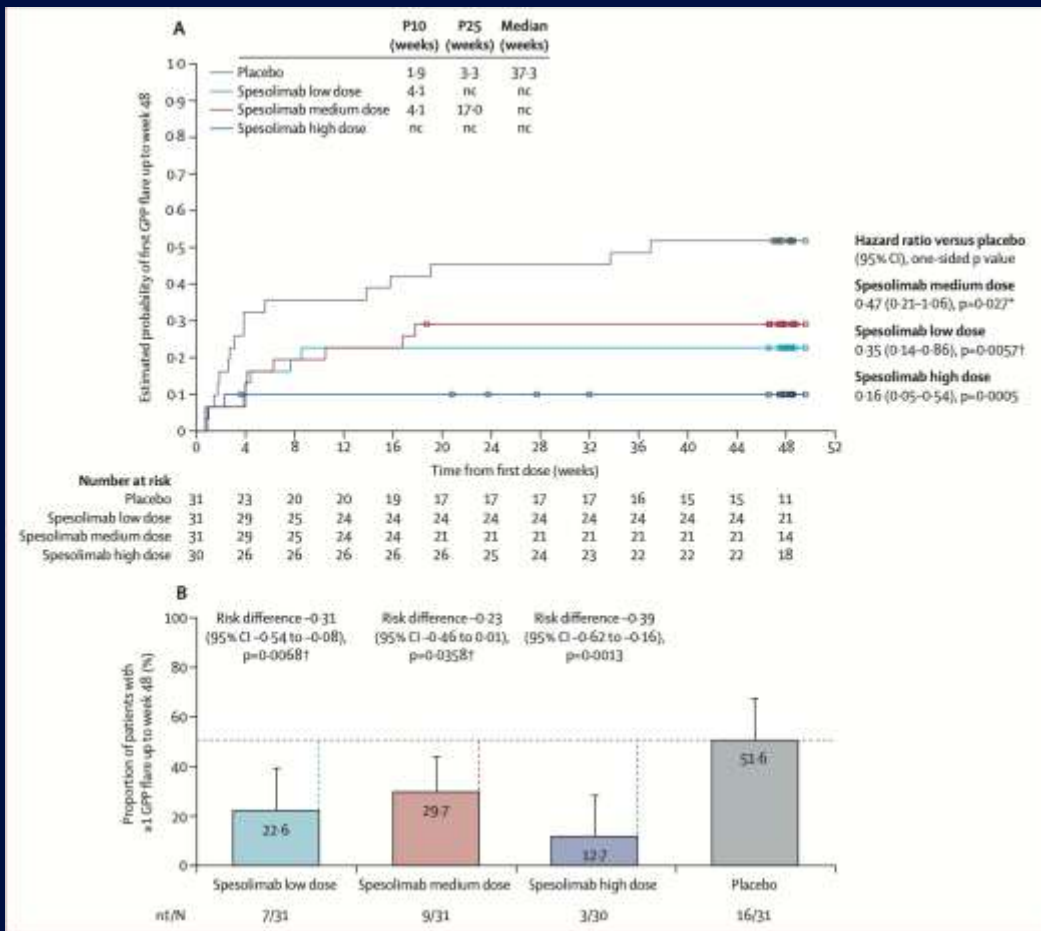
# Spesolimab and flare prevention

Morita Lancet 2023; 402: 1541

	Spesolimab			Placebo (n=31)
	Low (n=31)	Medium (n=31)	High (n=30)	
Sex				
Female	20 (65%)	20 (65%)	18 (60%)	18 (58%)
Male	11 (35%)	11 (35%)	12 (40%)	13 (42%)
Race				
Asian	20 (65%)	21 (68%)	21 (70%)	17 (55%)
White	11 (35%)	10 (32%)	9 (30%)	14 (45%)
Age, years	38.9 (16.5)	42.9 (16.7)	40.2 (16.4)	39.5 (14.0)
BMI, kg/m <sup>2</sup>	26.9 (7.2)	27.4 (8.8)	25.6 (7.3)	26.9 (8.3)
GPPASI total score	3.03 (3.48)	3.12 (4.16)	3.92 (4.42)	3.11 (2.81)
GPPGA total score				
0	2 (6%)	8 (26%)	3 (10%)	4 (13%)
1	29 (94%)	23 (74%)	27 (90%)	27 (87%)
PSS total score	4.1 (3.8)	3.9 (2.9)	5.3 (3.8)	3.6 (2.9)
DLQI total score	7.6 (6.7)	6.6 (5.6)	11.1 (6.9)	7.2 (5.6)
IL36RN mutation				
Yes	7 (23%)	10 (32%)	7 (23%)	4 (13%)
No	17 (55%)	15 (48%)	19 (63%)	22 (71%)
Unknown*	7 (23%)	6 (19%)	4 (13%)	5 (16%)
Concurrent plaque psoriasis at baseline†				
Yes	10 (32%)	7 (23%)	7 (23%)	10 (32%)
No	21 (68%)	24 (77%)	23 (77%)	21 (68%)
Use of at least one systemic medication for GPP (discontinued before randomisation)	25 (81%)	23 (74%)	22 (73%)	22 (71%)
Historical use of at least one biologic therapy	5 (16%)	8 (26%)	6 (20%)	9 (29%)
Historical number of flares per year	2.7 (2.3)	1.9 (0.9)	2.4 (1.9)	2.4 (1.2)
Time since first diagnosis				
≤1 year	5 (16%)	4 (13%)	4 (13%)	3 (10%)
>1 to ≤5 years	6 (19%)	9 (29%)	9 (30%)	10 (32%)
>5 to ≤10 years	6 (19%)	8 (26%)	8 (27%)	7 (23%)
>10 years	14 (45%)	10 (32%)	9 (30%)	11 (35%)

# Spesolimab and flare prevention

Morita Lancet 2023; 402: 1541



# *GPP Management Consensus*

- **GPP is a life-threatening disease that needs to be treated as quickly as possible**
- **The diagnosis is made based on clinical features**
- **Skin biopsy is not required for the diagnosis of GPP**
- **GPP classification criteria not required**
- **Timely access to therapy is crucial**

*Armstrong National Psoriasis Foundation, J Am Acad Dermatol 2024;90:727*

# *GPP Management Consensus*

- ❑ **Biologics are the treatment of choice**
- ❑ **IL36 inhibitors are recommended as first line treatment for acute flares**
- ❑ **IL17, IL23 and TNF inhibitors can be considered for acute flares**
- ❑ **High dose acitretin is recommended when biologics are not accessible**
- ❑ **Low dose acitretin or methotrexate is recommended for maintenance phase**

# *GPP summary*

- ❑ **An uncommon autoinflammatory disease**
- ❑ **Primary dysregulation of keratinocytes**
- ❑ **Systemic symptoms may predominate**
  - **Fever, cytokine syndrome, cholangitis**
- ❑ **Diagnosis is clinical**
- ❑ **Acute and chronic management required**
- ❑ **New role for IL36R blockade (spesolimab, imsidolimab, recibokibart)**



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