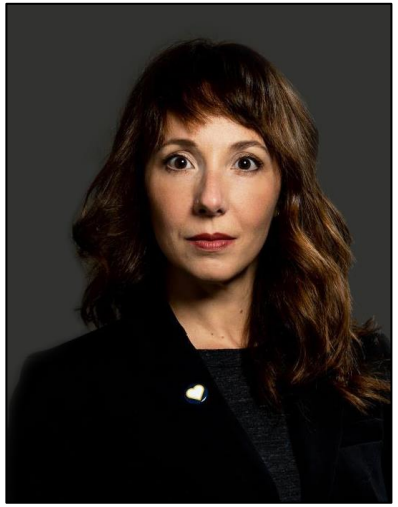
Provided by AAPA American Academy of PAs The France Foundation

Improving the Understanding, Diagnosis, and Management of

Generalized Pustular Psoriasis (GPP)

Steering Committee



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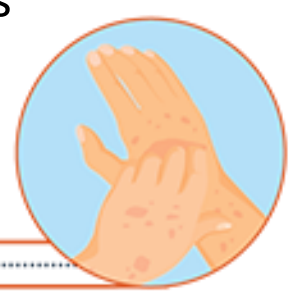
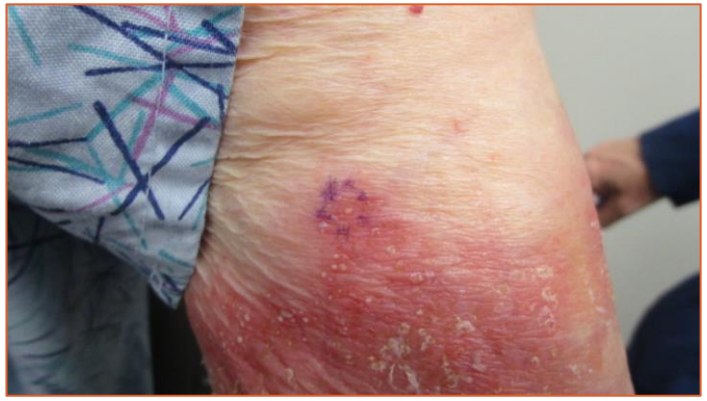


Learning Objectives

- Describe the pathophysiology of GPP related to other skin conditions such as plaque psoriasis
- Identify the diagnostic criteria for GPP and how they are used in diagnosing and assessing disease severity over time
- Identify comorbidities associated with GPP
- Recall the latest clinical research related to potential current and future options for the management of GPP
- Describe the burden of disease of GPP from a holistic standpoint, incorporating clinical and psychosocial elements including motivational interviewing to impact behavior change

The Pathophysiology of GPP

Case 1: Maggie



- 80-year-old female
- Medical history: psoriasis, hyperlipidemia, bipolar, hypertension, and lymphoma (remission)
- Medications: lamotrigine, rosuvastatin, apremilast, amlodipine, and triamcinolone ointment
- Social history: husband passed away one month ago
- Presents with ‘worsening of psoriasis’ and is asking for prednisone
- Denies constitutional symptoms: no fever, malaise, or joint pain

What should the HCP do next?

Pathophysiology of GPP

- Mechanism is not completely understood
- The main causes for GPP flares:
  - Genetics
  - Triggers
  - Inflammatory immune responses
- Genetics:
  - Mutations in the *IL36RN* gene which codes for IL-36 receptor antagonist (IL36RA)
- Other mutations in pro-inflammatory genes:
  - *CARD14* (caspase recruitment domain family member 14)
  - *AP1S3* (adapter protein family 1S3)

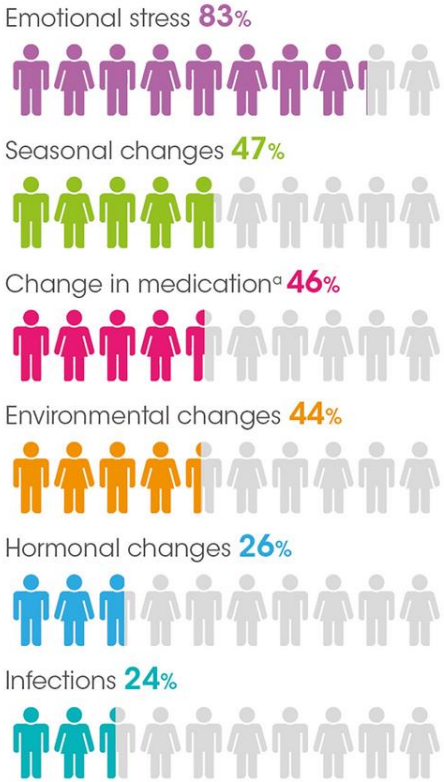
Flare Triggers	Types
Withdrawal	Corticosteroids or high potency topical steroids
Infections	• Streptococcus • Trichophyton rubrum • Cytomegalovirus • Epstein–Barr virus • Varicella zoster virus • Coronavirus 2019 (COVID-19) infections
Medications	• Oral steroids • COVID-19 vaccine • Betamethasone ointment • Calcipotriene ointment • Non-steroidal anti-inflammatory drugs (NSAID) • Progesterone • Terbinafine • Penicillin • Lithium • Iodine • Amoxicillin • Cyclosporine • Hydroxychloroquine • Anti-TNF and other biologics
Environmental factors	UV light
Other conditions	• Pregnancy (pustular psoriasis of pregnancy) • History of smoking • Menstruation • Hypocalcemia • Hypoparathyroidism • Stress

Patient Descriptions of Flares

Respondent definitions of a disease flare

Increased presence of...

Respondent perceptions for reasons for their disease flare



[a]Including stopping a current medication, a change in medication dose, or starting a medication.

How GPP impacts everyday activities during a flare versus not during a flare[b]

[b]Proportion of patients reporting a high impact on the activity in question (defined as 8–10 on a scale of 0–10).

Reisner DV, et al. *Am J Clin Dermatol*. 2022;23(Suppl 1):65-71.

Immunological Pathways Associated With GPP

- IL-36RA is an anti-inflammatory cytokine that regulates the influence of IL-36 on the immune system
- In patients with an *IL36RN* mutation, IL-36RA cannot bind and inhibit IL-36 leading to dysregulation of the immune system
  - Patients without an *IL36RN* mutation are believed to have an overactive IL-36 pathway due to other causes
- Dysregulation of the immune system and overactivation of IL-36 leads to a neutrophilic inflammatory response, resulting in keratinocyte proliferation and the formation of sterile pustules

Sugiura K. *Dermatol Ther (Heidelb)*. 2022;12(2):315-328.

Case 1: Discussion

- What symptoms does Maggie have that would lead to a diagnosis of GPP?
- What treatments should be avoided for *all patients* with psoriasis? (i.e. systemic corticosteroids)

Case 1: Resolution

- Maggie was placed on clobetasol ointment, advised to use under occlusion 2x daily
- Phone call to oncologist: Ok to move forward with ixekizumab
- Patient provided with samples due to inadequate coverage through Medicare
- Patient is responding well, and systemic symptoms were avoided with prompt treatment

Key Takeaways

- GPP is driven by mutation(s) in *IL36RN* a pro-inflammatory protein
  - Some patients do not have mutations in *IL36RN* and are thought to have overactivation of the IL-36 pathway via other mechanisms
- Inflammatory responses caused by dysregulation of the immune system and overactivation of IL-36 result in keratinocyte proliferation and sterile pustules
- GPP flares can be driven by withdrawal from corticosteroids or due to infections, medications, environmental factors, or comorbid conditions

Complexities of Diagnosing GPP

Case 2: Ray

- 55-year-old male
- Medical history: HTN, PsA
- Medications: losartan, adalimumab
- Recent health history:
  - Ray reports he saw his Rheumatologist one month ago for his adalimumab f/u. His Rheumatologist wanted him to f/u with dermatology due to a new onset 'rash.'
  - However, two weeks ago, the rash became more unbearable, so he visited Urgent Care. Ray was placed on a Medrol dose pack.
- Ray reports "spreading" of the rash from the hands and soles, and now involving his trunk and extremities

What are you next steps in diagnosing this patient?

https://dermnetnz.org/topics/generalised-pu
https://www.rarediseaseadvisor.com/features/recognizing-managing-flares-generalized-pustular-psoriasis/stular-psoriasis

Diagnostic Criteria

- Abrupt onset of widespread painful erythematous patches which become rapidly covered with tiny, pinhead size pustules
- Lakes of pus may result
- Erythroderma may occur
- May also have lower extremity edema, fever, malaise, arthralgias, jaundice, conjunctivitis, uveitis, and iritis
- May have a previous history of psoriasis and exposure to one of the known or unknown triggers

Mirza HA, Badri T, Kwan E. Generalized Pustular Psoriasis. [Updated 2022 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493189/

Confounding Issues in Diagnosing GPP

- GPP should be suspected in patients with acute onset widespread pustules on erythematous skin
- Previous medical history, including medication history, can provide clues
- Can progress rapidly and be LIFE THREATENING
  - Sepsis, liver, renal, respiratory failure, and death
- Can be mistaken for
  - Acute generalized exanthematous pustulosis
  - Secondarily infected atopic dermatitis
  - Generalized tinea corporis
- Traditionally considered a variant of PSO due to the occurrence of GPP in patients with a history of PSO
  - However, some GPP patients lack a previous hx of PSO
- New findings show GPP is genetically and histologically distinct from PSO

Mirza HA, Badri T, Kwan E. Generalized Pustular Psoriasis. [Updated 2022 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493189/

Pathological Confirmation

Procedure	Results
Wound culture and susceptibility of pustules	• Sterile
4 mm punch biopsy	• Psoriasiform changes in the epidermis (parakeratosis and elongation of rete ridges) • Numerous epidermal neutrophils and spongiform pustules of Kogoj
Blood test results	• Elevated erythrocyte sedimentation rate • Elevated C-reactive protein levels • An absolute lymphopenia at the onset, quickly followed by polymorphonuclear leukocytosis • Abnormally low plasma albumin, zinc, and calcium • Deranged lipid profile

Mirza HA, Badri T, Kwan E. Generalized Pustular Psoriasis. [Updated 2022 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493189/

Measuring Disease Severity

- Two tools provide assessment of the patient based on body surface involved and degree of erythema, desquamation, presence, number, and size or location of pustules
  - GPP Area and Severity Index (GPPASI)
  - GPP Physician Global Assessment (GPPGA)
- Tool for assessment of skin symptoms and systemic involvement
  - Japanese Dermatological Association Severity Index of GPP (JDA-GPPSI)

Burden AD, et al. *Am J Clin Dermatol*. 2022;23(Suppl 1):39-50.

Case 2: Resolution

- Patient placed on clobetasol ointment, applied under occlusion 2x daily
  - Topical corticosteroids used as adjunct therapy for pustular psoriasis can be beneficial, especially if used under occlusion
- Patient treated with spesolimab
- Patient well controlled re: Psoriasis (PsO)

Key Takeaways

- Clues to the diagnosis can sometimes be found in the medical and medication history
- Wound cultures show sterile pustules
- GPP is genetically and histologically different than PSO
- GPP can rapidly progress and be life threatening

Chronicity and Comorbidities: Considerations for Disease Management Over Time

Case 3: Bill

- 54-year-old white male
- Medical history: hypertension, obesity, smoking, and mild scalp psoriasis
- Current medications: lisinopril 10 mg daily and clobetasol solution PRN for his scalp rash
- Recent health history:
  - Presents to his primary care provider with a 2-day history of “the worst itching of my entire life”
  - Erythematous rash with scale noted on the trunk, buttocks, arms, legs, hands, and feet
  - Patient is afebrile, nauseated, and is not sleeping. He reports a headache along with joint pain and extreme sensitivity involving his fingertips and feet that make it difficult to function

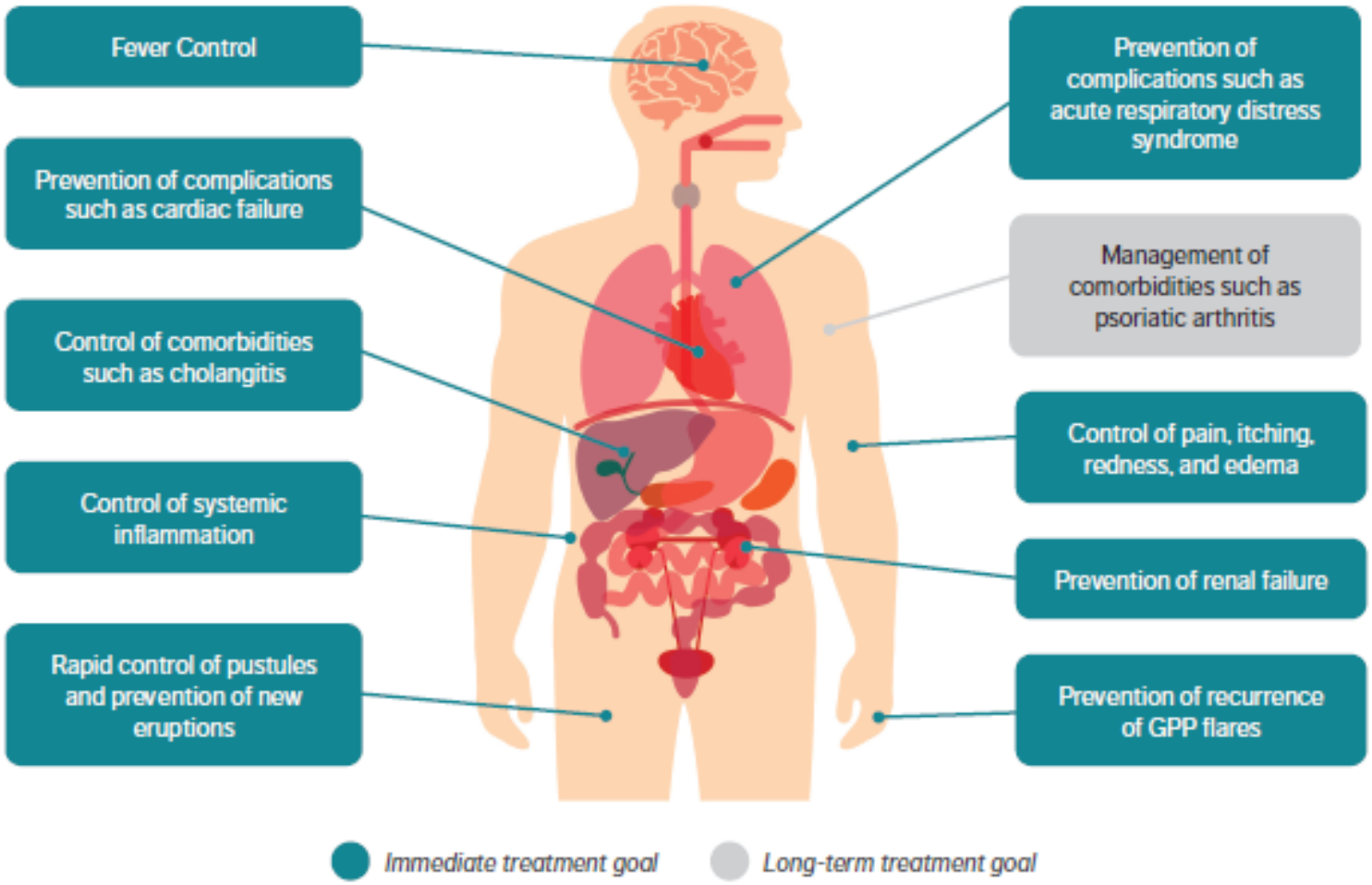
How should this patient’s symptoms be evaluated and documented?

Physical Exam

- Patient's skin is bright red and tender
- Marked scale involving the flexural areas, genitals, palms, and soles
- Numerous 2-3 mm pustules appear diffusely on the trunk, palms, and soles
- Marked "sausage-shaped" digits (dactylitis) on several fingers and toes that are painful on palpation
- Missing fingernails on several swollen fingers (anonychia)

Is there any additional testing that should be ordered for this patient?
What would the differential diagnosis be?

Assessing Severity and Changes Over Time

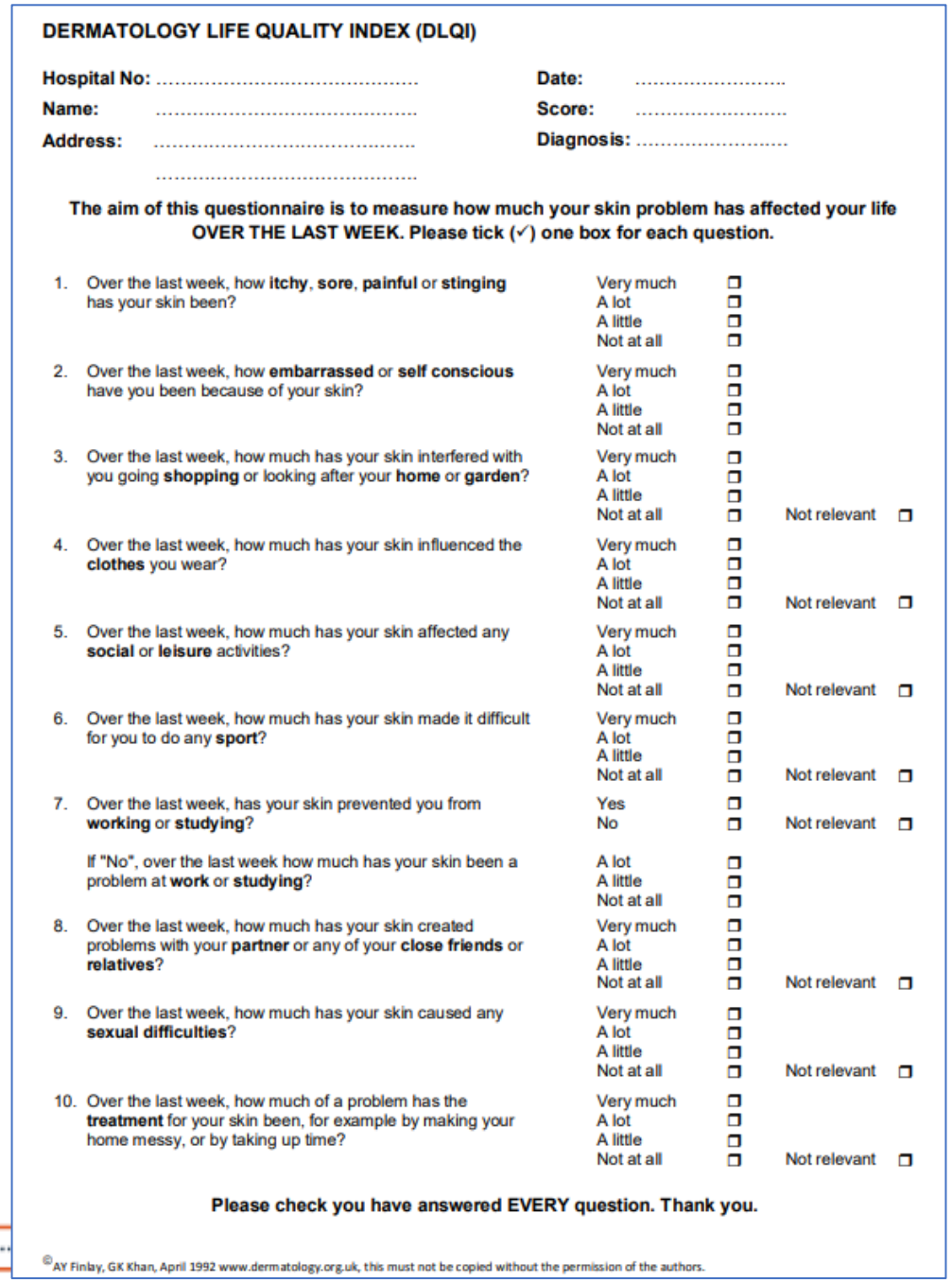


Krueger J. *Am J Clin Dermatol*. 2022;23(Suppl 1):51-64.

Dermatology Life Quality Index

- Patient completed questionnaire
- Scores
  - 0-1 no effect on QoL
  - 2-5 small effect on QoL
  - 6-10 moderate effect on QoL
  - 11-20 very large effect on QoL
  - 21-30 extremely large effect on QoL
- DLQI allows clinicians to gain a more accurate picture of individual patients' quality of life. This can lead to more appropriate clinical interventions depending on the severity of impairment

Finlay AY and Khan GK. *Clin Exp Dermatol* 1994; 19:210-216.



DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....
Name: ..... **Score:** .....
Address: ..... **Diagnosis:** .....
.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ❒ No ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ❒ A little ❒ Not at all ❒		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.

Case 3: Resolution

- Dermatology Life Quality Index (DLQI) = 14 (significant effect on quality of life)
- Radiographs reveal fusiform soft tissue swelling and periostitis of second and third digits of the right hand; second digit of the left hand; and fourth digit of the left foot
- Lab tests are normal, except for hypocalcemia
- Patient received spesolimab 900 mg via infusion (Dose #1) and was also placed on an oral steroid taper
  - Topical clobetasol solution to his fingertips for pain relief
  - Supplemental oral calcium
- One week later, his rash and symptoms were improved but some erythema persisted on his hands, feet, and right abdomen
  - Due to incomplete response, patient received spesolimab 900 mg via infusion
- 2 weeks later:
  - Patient presented with no active inflammatory rash
  - Joint pain and swelling has resolved
  - Working on smoking cessation

Key Takeaways

- It is important to assess severity and changes over time for patients with GPP to prevent future flares and complications
- The DLIQ allows clinicians to better understand the impact of GPP on the QoL of patients

Current and Emerging Treatments for GPP

Current Treatment Options

Topical therapies

Corticosteroids

Traditional systemic agents

Biologics

GPP Topical Therapies

- Topical calcipotriene and topical tacrolimus
- Wet wraps containing triamcinolone
- Photochemotherapy with psoralen and UV light
- Topical therapies **should not be used alone** in patients with GPP, especially among patients with more severe disease

Systemic Corticosteroids

- Fast onset of action
- Oral corticosteroids can be used short term during acute flares
- Caution in pregnant women
  - Risk of cleft palate when used during first trimester of pregnancy
- Dose tapering is necessary as rapid withdrawal of systemic corticosteroids may induce a GPP flare

First-line Systemic Therapies for Acute Flares

Agent	Treatment Type	Benefits	Risks
Acitretin	Retinoid (oral)	• Onset of action in days/weeks	• Teratogenic • Long-term use can cause osteoarticular symptoms • Can adversely affect bone growth in children
Cyclosporine	Calcineurin inhibitor	• Best for severe, acute disease • Onset of action in days/weeks	• Caution in pregnant women • Long-term use can cause hypertension and renal dysfunction • Must monitor blood pressure, renal function, and immunosuppression
Methotrexate	Disease-modifying anti-rheumatic drug	• Recommended for patients unresponsive to/intolerant of retinoids	• Abortifacient, mutagenic, and teratogenic • Hepatotoxicity and hematologic toxicity • Slow onset of action (weeks)

Strober B, et al. *Dermatol Ther (Heidelb)*. 2022;12(2):381-393.

Biologic Therapies

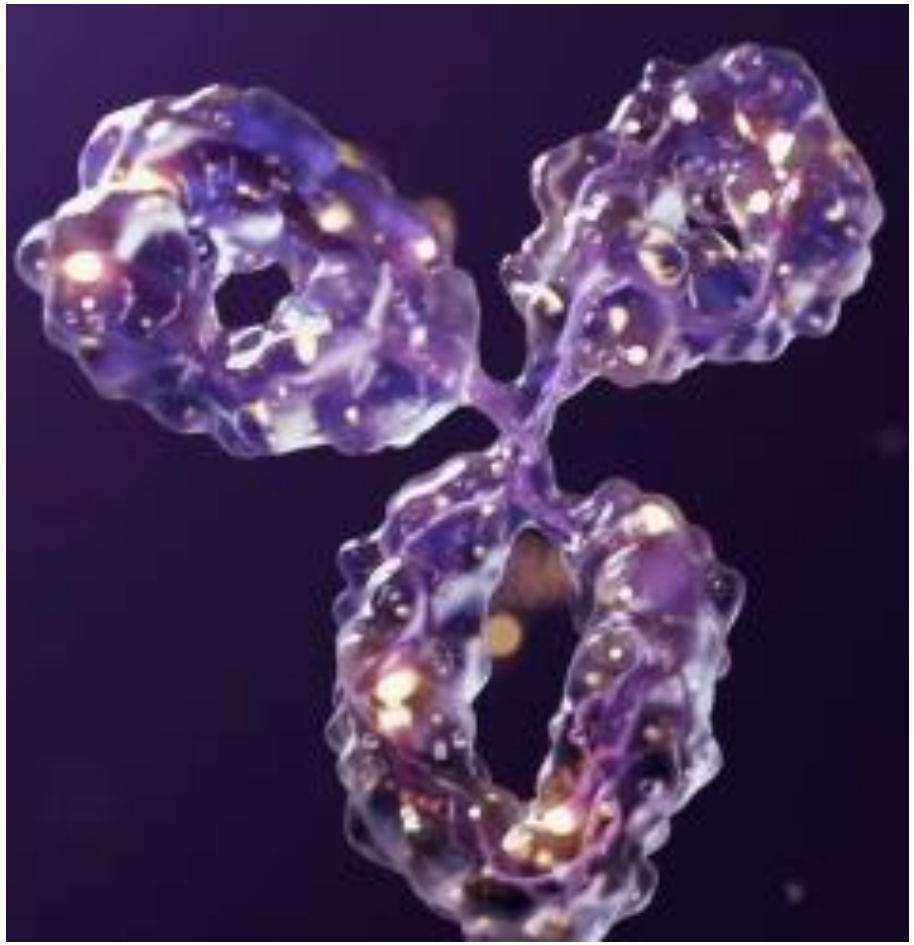
✓ Preventative
✓ Acute Flares

Class	Agent
IL-36R inhibitors	• Spesolimab ✓✓ • Imsidolimab (Being investigated in clinical trials as of 2019) ✓✓
TNFa inhibitors	• Adalimumab ✓✓ • Certolizumab pegol ✓✓ • Etanercept ✓✓ • Infliximab ✓
IL-17/IL-17R inhibitors	• Brodalumab ✓✓ • Ixekizumab ✓ • Secukinumab ✓✓ • Bimikizumab ✓✓
IL-12/IL-23 inhibitors	• Guselkumab ✓✓ • Risankizumab ✓✓ • Ustekinumab ✓✓
IL-1 inhibitors	• Anakinra (Being investigated in clinical trials as of 2023) ✓✓ • Canakinumab ✓✓ • Gevokizumab ✓✓

National Psoriasis Foundation. www.psoriasis.org/pustular; Krueger J, et al. *Am J Clin Dermatol*. 2022;23(Suppl 1):51-64.

Targeted Therapies

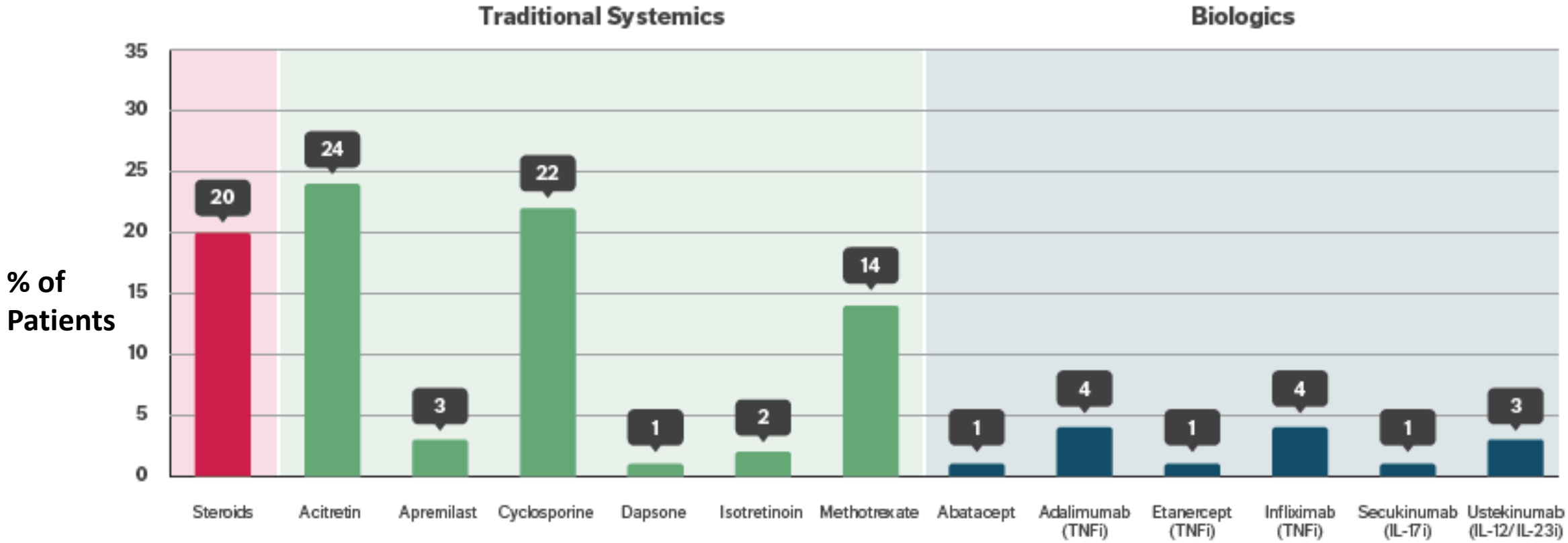
- Spesolimab is the only FDA-approved therapy for the treatment GPP flares in adults
  - Humanized selective antibody that blocks the activation of IL-36R
- 84% reduction in GPP flares up to 48 weeks relative to placebo in clinical trials
- Only available as an infusion
  - Subcutaneous form is currently being investigated
- Imsidolimab (IL-36 inhibitor) is currently being investigated for its use in the treatment of GPP



Mullard A. *Nat Rev Drug Discov*. 2022;21(11):786.

GPP Real-world Use

In a retrospective, longitudinal case series of adults (≥18 years) with a diagnosis of GPP confirmed by a dermatologist, patients received the following therapies:



N = 95

Noe MH. *JAMA Dermatol*. 2022;158(1):73-78.

Key Takeaways

- GPP has a profound short- and long-term impact on patients
- Topical therapies alone are insufficient in patients with GPP and should always be combined with systemic/biologic agents
- There are a variety of biologic agents that have demonstrated efficacy in patients with GPP, although only one (spesolimab) is specifically indicated for this population

Engaging Patients in the Long-term Management of GPP

Burden of GPP for Patients According to an Online Survey

- Approximately 33% of GPP patients experience flares for months to years prior to an accurate diagnosis
  - 59% of patients state the delay was due to misdiagnosis
  - 51% visited multiple healthcare providers before being properly diagnosed
  - Some report lack of affordable healthcare and access to specialists as contributing factors
- 71% GPP patients live in fear of another flare
  - Many experience fever and substantial pain with each flare
- 65% GPP patients live in fear their medication will stop working
- 59% GPP patients report feelings of hopelessness and depression during their flares

Reisner DV, et al. *Am J Clin Dermatol*. 2022;23(Suppl 1):65-71.

Motivational Interviewing

- A style of communication that focuses on listening without judgement to discuss **if** the person wants to make a change, **why**, and **what barriers** they perceive
- Acknowledges that **the person is the expert of their own life**
- **Engage:** Create a partnership with the patient. Listen, reflect what they say and their experiences, support autonomy.
- **Focus:** Decide on an agenda together so that you can move to the topic of change
- **Evoke:** The "why." Discussion on the person's goals and reservations. It's normal for a person to have mixed feelings about change, normalize that and explore.
- **Plan:** Is the person ready to make a change? If so, this step is the "how" of making the change. Reaffirm the person wants to make a change and come to a plan together, incorporating the person's life and experiences.

For a deeper diver on change, seek out "Prochaska and DiClemente Transtheoretical Model/ Stages of Change"

At all times, you are partnered with the patient, not instructing them

Motivational Interviewing Network of Trainers. Understanding Motivational Interviewing. https://motivationalinterviewing.org/understanding-motivational-interviewing. Accessed August 22, 2023

Riess H, Kraft-Todd G. *Acad Med*. 2014;89(8):1108-1112.

Communication Tips

- Use open-ended questions to hear the person's story in their own words
- Don't interrupt
- Display empathy
  - Eye contact, muscles or facial expression, posture, affect, tone of voice, hearing the whole patient, and your response
- Be a partner; the person is the expert on themselves
- Ask and listen: What are their goals, priorities, values, and barriers to change and success?
- Repeat/rephrase what the person has said to demonstrate you have heard them
- Respect reasons and choices without judgement
- Point out times the person has shown effort, had success, or shown determination. Positively reinforce those efforts with your words.
- Focus on the words they use that support change, instead of the words that support keeping things the same
- Respond to what they are saying. This should be an equal conversation. You are both experts!

Motivational Interviewing Network of Trainers. Understanding Motivational Interviewing. https://motivationalinterviewing.org/understanding-motivational-interviewing. Accessed August 22, 2023
Riess H, Kraft-Todd G. *Acad Med*. 2014;89(8):1108-1112.

Key Takeaways

- Like many other chronic disease, GPP has a significant impact on QoL
- Learning about this disease state will increase awareness and result in patients being diagnosed accurately and promptly
- Approaching all patients with the mindset of a partnership is key to helping them identify areas of change and to impact improved disease management and QoL

Thank you!