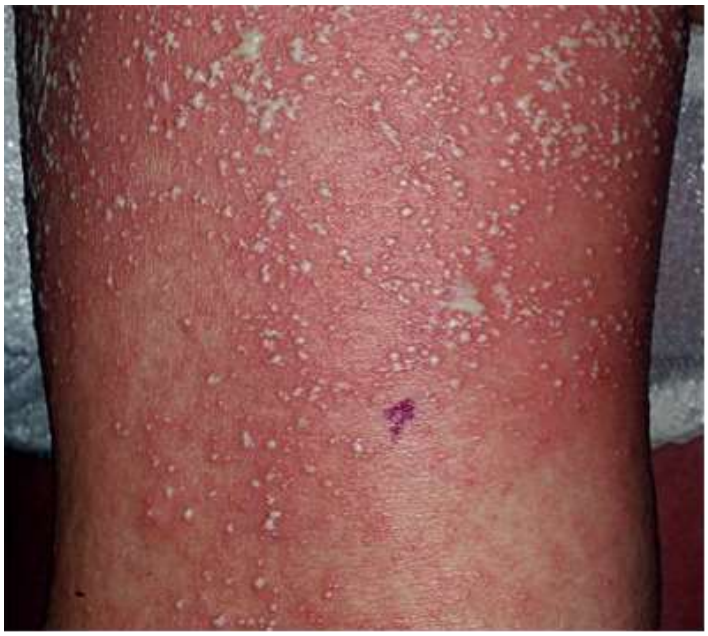
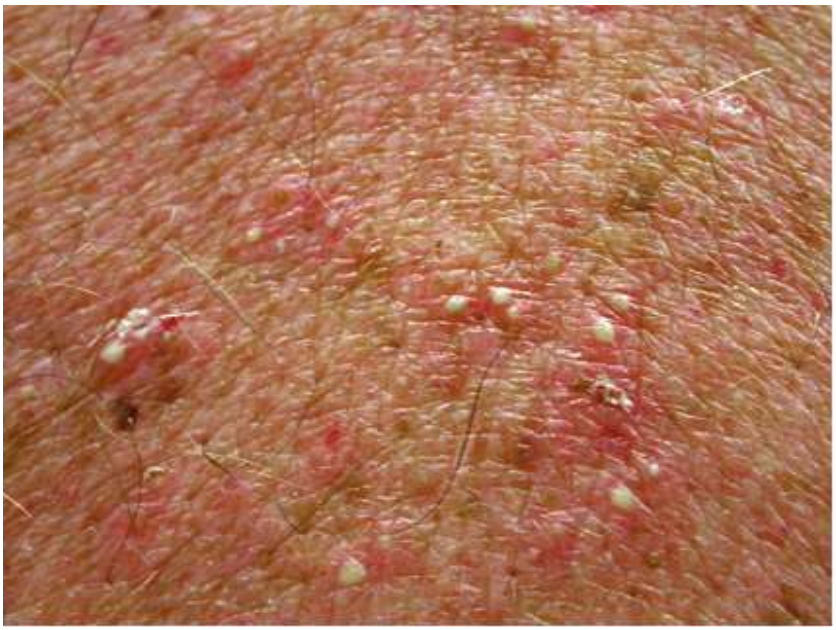
# ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)





*Left: Confluent non-follicular pustules superimposed on oedematous erythema in a 46 year old woman with AGEP. Right: Non- follicular, pinhead-sized pustules on a background of edematous erythema are characteristic of AGEP, (Werner Pichler, Up to Date Website).*

## Introduction

**Acute Generalized Exanthematous Pustulosis (AGEP)** is a rare, acute skin eruption characterized by the development of numerous non-follicular superficial **sterile pustules** on a background of edematous erythema.

Other terminology includes, *pustular drug eruption* and *toxic pustuloderma*.

It is caused by a **drug reaction** in > 90 % of cases.

Less commonly it is due to viral infections.

When the causative agent is withdrawn, AGEP resolves spontaneously without sequelae in the majority of patients, however in small number of patients disease can be severe with a mortality rates of 2 - 4 percent.

## Epidemiology

AGEP is rare.

It can occur at any age, although it most often affects adults with a mean age of 56 years.

## Pathophysiology

AGEP is a T cell mediated neutrophilic inflammation involving drug-specific CD4+ T cells, cytotoxic CD8+ T cells, and inflammatory cytokines and chemokines.

Recent research suggests that AGEP is associated with IL36RN gene mutations.

These genetic abnormalities make the patient more susceptible to pustulosis when prescribed certain medications or when exposed to infection.

Similar mutations are also found in some patients with other pustular disorders such as generalised pustular psoriasis and palmoplantar pustulosis

### *Causes*

The causes of AGEP include:

1. Drugs are by far the commonest cause, (> 90 % of cases):

   The strongest associations are with:

   - Antibiotics, principally the beta lactam antibiotics.
   - Calcium channel blocker: particularly diltiazem.
   - Anti-malarials

2. Viral infection:

   Viral infections can be triggers of AGEP especially in children.

   Many have been implicated including:

   - Epstein-Barr virus
   - Enterovirus
   - Adenovirus
   - Cytomegalovirus
   - Hepatitis B virus

3. Idiopathic:

- In some cases a clear cause is never identified.

## Clinical features

The onset of AGEP is rapid and occurs within **hours to 2 days** of exposure to the causative drug.

It usually resolves spontaneously in about 10 - 14 days after the offending agent is ceased.

It does not usually recur, unless the same medication that caused a first episode is taken again.

When the causative agent is withdrawn, AGEP resolves spontaneously without sequelae in the majority of patients, however in small number of patients disease can be severe with a mortality rates of 2 - 4 percent. [2]

Clinical features include:

1. AGEP may be associated with non-specific constitutional symptoms:

   - Fever
   - Malaise/ lethargy
   - Generally the patient is not particularly unwell.

2. Rash:

   - AGEP is characterised by the **rapid appearance** of areas of red skin studded with small sterile pustules (small blisters filled with white/yellow fluid).
   - Typically the AGEP rash starts on the face or in the axillae and groin, and then becomes more widespread.
   - There tends to be more disease in skin folds.
   - Facial swelling often arises.
   - Palmar and plantar involvement is common
   - The rash may last for 1-2 weeks and then the skin desquamates off as it resolves.

- There is usually rapid resolution of the rash after drug discontinuation.

- Involvement of mucous membranes is *unusual* and, when present, is limited to erosions of the lips.

3. Organ involvement is **not** common in AGEP, but can occur, particularly in older or compromised patients.

   A mild increase in serum transaminases or a reversible reduction in the creatinine clearance have been reported in some patients

*Differential diagnosis:*

Principally these will be:

1. SJS-TEN:

   - Severe cases of acute generalized exanthematous pustulosis (AGEP) may be difficult to differentiate from SJS- TEN.

     Severe cases of AGEP presenting with atypical target lesions and confluent pustules mimicking a positive Nikolsky sign may be difficult to differentiate from Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

     Features that favour a diagnosis of SJS/TEN include:

     ♥ A longer latency between drug exposure and clinical manifestations (one to four weeks);

     ♥ Involvement of the mucous membranes (in over 90 percent of cases)

     ♥ More severe course

     ♥ Histologic finding of full thickness epidermal necrosis with a sparse inflammatory dermal infiltrate.

2. Generalized acute pustular psoriasis:

   - Seen at a single time point and without additional information, generalized acute pustular psoriasis and AGEP may be difficult to differentiate both clinically and histologically.

     Criteria that favour a diagnosis of generalized acute pustular psoriasis include a **history of psoriasis**; longer duration of fever and pustular eruption; **absence of drug exposure**; and **histologic finding** of subcorneal pustules with acanthosis and papillomatosis.

Although generalized acute pustular psoriasis can sometimes be elicited by drugs, the spectrum of medications known to trigger psoriasis (mainly beta-blockers or lithium) differs from the drugs associated with AGEP.

3. Bullous impetigo:

- Bullous impetigo generally occurs in young children.

  Small vesicles or pustules are usually localized to the head and neck or intertriginous areas.

  Pustules rupture and leave erosions with a honey-colored crust.

  Gram staining of pustule smear reveals Gram-positive cocci. Culture of pustule exudate is positive for Staphylococcus aureus.

4. DRESS with pustules:

- Pustules can occasionally occur in patients with drug reaction with eosinophilia and systemic symptoms (DRESS).

  However, DRESS is characterized by:

  - ♥ A long latency (2-8 weeks) between drug exposure and appearance of symptoms
  - ♥ A more severe and prolonged clinical course than AGEP
  - ♥ Eosinophilia or atypical lymphocytosis in the peripheral blood
  - ♥ Signs and symptoms of visceral involvement (abnormal liver function tests in > 90 percent of cases).
  - ♥ Different histology.

## **Investigations**

The diagnosis of AGEP is based upon the clinical presentation and histologic examination of a skin biopsy.

The rapid resolution of the eruption after drug discontinuation also supports the diagnosis.

*Blood tests:*

1. FBE:

- Leukocytosis with marked neutrophilia (> 7000 / microL).

2. CRP

3. U&Es/ glucose.

*Skin biopsy:*

Histologic examination of a skin biopsy is necessary to confirm the diagnosis and rule out other causes of pustular eruptions.

Skin lesion biopsy shows spongiform sub-corneal and/or intraepidermal pustules filled with **neutrophil infiltration.**

*Swab for M&C:*

Gram staining of a pustular smear and culture of pustule exudate may be helpful in excluding a superficial bacterial skin infection.

*Skin Patch Testing:*

Skin Patch Testing with one or multiple suspected drugs may be useful in identifying the cause of AGEP.

Patch testing is generally performed 4-6 weeks after the disease resolution.

A positive test can confirm a suspected drug as the cause of AGEP. However, a negative result does not exclude that a certain drug is the causative agent.

A positive patch test reaction is often morphologically similar to AGEP, showing small sterile pustules on an erythematous base. Systemic reactions to patch testing rarely have been reported.

## Management

1. **Cease any likely causative agent:**

   - Immediate withdrawal of the causative agent is the mainstay treatment of AGEP.

     In patients taking multiple drugs, the drugs suspected to be the cause of AGEP should be discontinued.

   - Since re-exposure to the causative agent can induce another episode of AGEP, patients should be counselled to avoid the offending drug and be provided with a written list of the generic and brand names of the offending drug.

2. IV fluids:

    - Older or compromised patients with fever and widespread eruption may require fluid, electrolyte, and nutritional support.

3. Skin care:

    - In the **pustular phase**, **moist dressings and antiseptic solutions** may be used for relief of pruritus and prevention of bacterial superinfection.

    - In the **desquamation phase**, **emollients** may be helpful in restoring the skin barrier function.

4. Oral antihistamines

5. Analgesics

6. Corticosteroids:

    - Topical

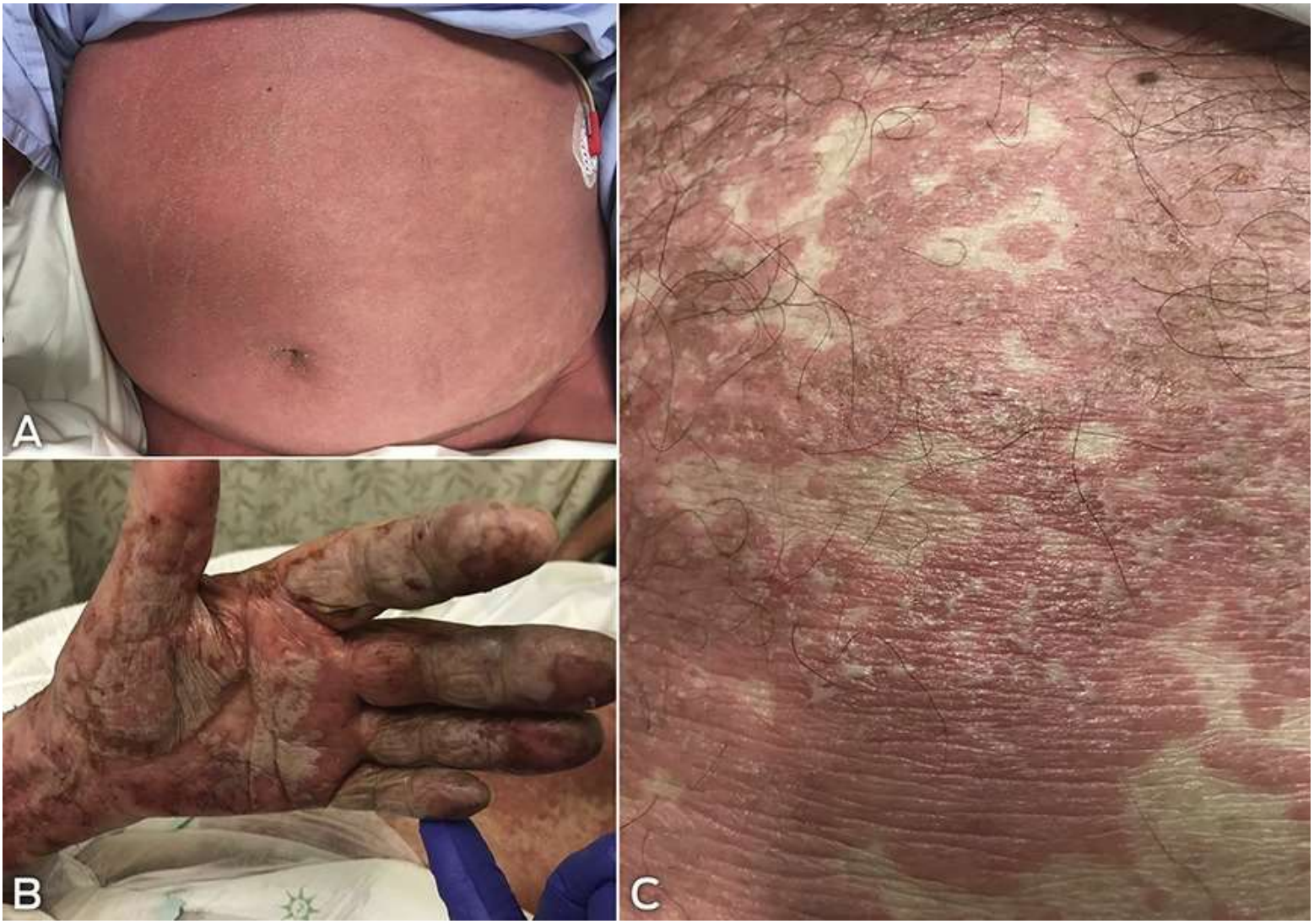
    - Oral systemic therapy for more severe cases.

*Disposition:*

AGEP is an uncommon condition and suspected cases should be referred to the Dermatology Unit.

Patients with **severe** forms of AGEP are **hospitalized** for treatment.

## Appendix 1




*Hundreds of coalescing superficial pustules on an erythematous background appear rapidly (A, B). Palmar and plantar involvement is common (C).*

*References*


1. Diana Purvis; Acute generalized exanthematous pustulosis (AGEP) in DermNet NZ Website, September 2015.

    - www.dermnetnz.org

2. Alexis Sidoroff et al. Acute generalized exanthematous pustulosis (AGEP) in Up to Date Website 18 March 2015.

3. Paul Chee; Recognising severe cutaneous adverse drug reactions. MJA 207 (8) 16 October 2017.

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