

# Acute generalized exanthematous pustulosis (AGEP): A review and update

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Acute generalized exanthematous pustulosis is a severe cutaneous adverse reaction characterized by the rapid development of nonfollicular, sterile pustules on an erythematous base. It is attributed to drugs in the majority of cases. Antibiotics are the most common cause of acute generalized exanthematous pustulosis; however, a wide variety of drugs has been associated with this condition. Typically, within 48 hours of ingesting the causative medication, there is acute onset of fever and pustulosis with leukocytosis. In severe cases there can be mucous membrane and systemic organ involvement. Histologic findings include intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophils and eosinophils. Treatment focuses on removal of the causative drug, supportive care, infection prevention, and the often beneficial use of a potent topical steroid. (J Am Acad Dermatol 2015;73:843-8.)

**Key words:** acute generalized exanthematous pustulosis; drug allergy; pustular drug eruption; pustules; severe cutaneous adverse reactions; T cells.

## HISTORY

Acute generalized exanthematous pustulosis (AGEP) was originally classified as a form of pustular psoriasis. In 1968, Baker and Ryan<sup>1</sup> suspected AGEP was a separate entity unassociated with psoriasis. In 1980, Beylot et al<sup>2</sup> proposed the name “acute generalized exanthematous pustulosis” to describe the disease. AGEP is one of the severe cutaneous adverse reactions that include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).<sup>3-7</sup>

## ETIOLOGY

AGEP is an adverse drug reaction most commonly associated with the following drugs: pristinamycin (an antistaphylococcal medication used in Europe), aminopenicillins, quinolones, hydroxychloroquine, sulfonamides, terbinafine, diltiazem, ketoconazole, and fluconazole.<sup>8-11</sup> The time period from drug exposure to reaction onset is typically within 48 hours, with antibiotics having a median of 24 hours.<sup>8</sup> Infectious agents such as parvovirus B19,<sup>12</sup>

### Abbreviations used:

AGEP:	acute generalized exanthematous pustulosis
DRESS:	drug reaction with eosinophilia and systemic symptom
IL:	interleukin
INF:	interferon
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis

*Chlamydia pneumoniae*,<sup>13</sup> and cytomegalovirus<sup>14</sup> are infrequently related etiologically. Additional causes of AGEP, such as contact with mercury<sup>15</sup> and spider bites,<sup>16</sup> have been described.

## PATHOPHYSIOLOGY

The pathophysiology of AGEP has been investigated by using patch tests<sup>17-20</sup> and in vitro tests,<sup>21,22</sup> which have suggested that AGEP is a T cell–mediated disease. After exposure to the causative agent, antigen-presenting cells present the cognate antigen using MHC molecules, causing activation of specific CD4 and CD8 T cells. Once activated, these T cells, referred to as drug-specific T cells, proliferate and

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then migrate into the dermis and epidermis. The drug-specific CD8 T cells use perforin/granzyme B and Fas ligand mechanisms to induce apoptosis of keratinocytes within the epidermis, leading to tissue destruction and epidermal vesicle formation.<sup>19</sup> During the initial stage of AGEP the vesicles are composed mainly of drug-specific CD4 T cells and keratinocytes. These cells release increased amounts of CXCL8, a potent neutrophilic cytokine, leading to the chemotaxis of neutrophils into the vesicles, causing the transformation of vesicles into sterile pustules.<sup>18</sup>

Analysis of drug-specific CD4 T cells from patients with AGEP shows a predominant Th1 type cytokine profile with increased interferon (INF)- $\gamma$  and granulocyte/macrophage colony-stimulating factor production.<sup>20</sup>

Increased secretion of interferon- $\gamma$  and granulocyte/macrophage colony-stimulating factor leads to augmented neutrophil survivability, which enhances formation of sterile pustules. INF- $\gamma$  and granulocyte/macrophage colony-stimulating factor may induce the release of CXCL8 by keratinocytes, which further leads to neutrophil accumulation.<sup>18</sup> In some patients with AGEP there are occasionally CXCL8 producing CD4 T cells that demonstrate a Th2 cytokine pattern with high interleukin (IL)-4 and IL-5 production.<sup>20</sup> Increased IL-5, a potent stimulator of eosinophil growth and differentiation, may explain the eosinophilia seen in approximately 30% of AGEP cases. Th17 cells may also play a role in the development of AGEP, as Th17 cells release IL-17 and IL-22, which have a synergistic effect on keratinocytes' production of CXCL8.<sup>23,24</sup> Analysis of peripheral blood from patients with AGEP revealed high levels of Th17 cells with elevated IL-22.<sup>25,26</sup>

Genetic mutations may predispose individuals to develop AGEP. Mutations in the IL-36 receptor antagonist (IL36RN) gene have been linked to generalized pustular psoriasis.<sup>27</sup> Because of the clinical and immunologic similarities between generalized pustular psoriasis and AGEP, there have been several investigations of IL36RN gene mutations in AGEP. The IL36RN gene encodes the IL-36 receptor antagonist, a molecule that blocks inflammatory cytokines such as IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$ .<sup>28</sup> A mutation in the IL36RN gene leads to decreased or ineffective IL-36 receptor antagonist, resulting in an uncontrolled IL-36 pathway. Increased IL-36 signaling leads to increased

production of IL-6, IL-8, IL-1 $\alpha$ , and IL-1 $\beta$  and might predispose to pustular eruptions. IL36RN gene mutations were found to be significantly higher in patients with AGEP compared with a control population (1.6% vs 0.4%).<sup>29</sup> The patients with AGEP and IL36RN gene mutations were more likely to have lip or oral involvement versus patients with AGEP without the

gene mutation. These results suggest that patients with the IL36RN gene mutation are predisposed to developing AGEP.

### CAPSULE SUMMARY

- Acute generalized exanthematous pustulosis is a severe cutaneous adverse reaction with rapid onset.
- Systemic involvement with hepatic, renal, or pulmonary insufficiency occurs in approximately 20% of cases.
- Treatment involves discontinuation of the drug and monitoring for systemic involvement and bacterial superinfection.

### CLINICAL FEATURES

The mucocutaneous features of AGEP include tens to hundreds of small, sterile, nonfollicular pustules on an erythematous base with no or minimal mucous membrane involvement. The distribution favors the trunk and intertriginous regions. AGEP

is typically pruritic. If there is mucous membrane involvement, it is usually confined to a single site, most often the lips or buccal mucosa. Leukocytosis with an elevated neutrophil count ( $>7.5 \times 10^9/L$ ) and fever ( $\geq 38^\circ C$ ) are features of AGEP. In a study of 58 patients, 17% of cases had internal organ involvement. Hepatic, renal, and pulmonary dysfunction were the most common features in patients with systemic involvement.<sup>30</sup> Hepatic involvement includes elevated enzymes in either a hepatocellular pattern with high aspartate aminotransferase and alanine aminotransferase or a cholestatic pattern with elevated alkaline phosphatase and  $\gamma$ -glutamyltransferase. Abdominal ultrasound of individuals with hepatic involvement may reveal steatosis or hepatomegaly.<sup>30,31</sup> Pulmonary involvement includes bilateral pleural effusion resulting in hypoxemia, requiring supplemental oxygen. Multiple organ dysfunction in AGEP may occasionally require treatment in an intensive care unit.<sup>30,32,33</sup> Elevated absolute neutrophil count and C-reactive protein levels were associated with systemic organ involvement.<sup>30</sup> Upon discontinuation of the causative agent, resolution of the cutaneous features typically occurs within a few days.<sup>34</sup> During resolution of AGEP, there is desquamation over the affected area. Mortality is less than 5% in AGEP. When death does occur, it is typically a result of multiple organ dysfunction and disseminated intravascular coagulation. Those at highest risk of death have comorbidities and diffuse or mucous membrane involvement<sup>35-37</sup> (Figs 1 and 2).



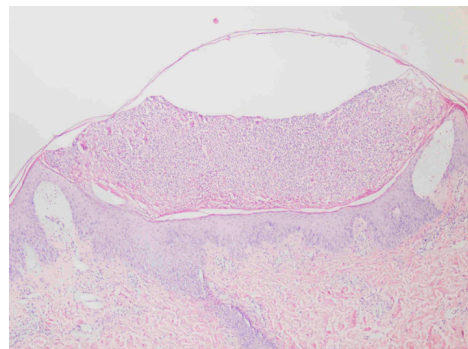
**Fig 1.** Acute generalized exanthematous pustulosis with widespread nonfollicular pustules on edematous erythema. Courtesy of Giuseppe Micali, Dermatology, University of Catania, Italy.



**Fig 2.** Acute generalized exanthematous pustulosis during resolution with widespread desquamation of the arm.

## HISTOLOGY

Histologic features of AGEP are characterized by intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophilic and eosinophilic infiltrates.<sup>10,38,39</sup> The majority of intraepidermal pustules are located in the upper epidermis, often contiguous with the subcorneal pustules. The pustules tend to be large and contain eosinophils. Spongiform changes occur in both the intracorneal and subcorneal pustules. Epidermal changes also include spongiosis with exocytosis of neutrophils and necrotic keratinocytes. Certain histologic features of plaque-type psoriasis, such as increased mitotic figures and tortuous, dilated blood vessels, are infrequent in patients with AGEP. In a study of 102 cases, there was no statistically significant difference in histopathology between a subgroup of AGEP with a personal history of psoriasis as compared with AGEP with no history of psoriasis<sup>38</sup> (Fig 3).



**Fig 3.** Acute generalized exanthematous pustulosis. Histologic view of subcorneal pustule and papillary dermis edema. (Hematoxylin-eosin stain; original magnification:  $\times 40x$ .)

## DIAGNOSIS

Diagnosis of AGEP depends on clinical and histologic criteria. An AGEP validation score was developed by the EuroSCAR group.<sup>8,40</sup> It is a standardized scheme based on morphology, clinical course, and histology that classifies patients with suspected AGEP as having definite, probable, possible, or no AGEP. A drug patch test can be used to identify the cause of AGEP when the responsible drug is unclear<sup>41</sup> (Table I).

## DIFFERENTIAL DIAGNOSIS

AGEP is characterized by nonfollicular pustules, which distinguishes it from follicular pustular diseases such as bacterial folliculitis. Other nonfollicular pustular diseases, including pustular psoriasis, can be more difficult to discern from AGEP. Pustular psoriasis is slower in onset, its pustules occurring on top of an erythematous base. Often, the pustules coalesce into large purulent collections. Generalized pustular psoriasis has been associated with pregnancy, drugs, and infection. In addition, there is often a personal or family history of psoriasis. Histologic findings of pustular psoriasis include parakeratosis, increased mitotic figures, Munro microabscess, and tortuous, dilated blood vessels.<sup>38</sup> DRESS typically has an erythematous morbilliform rash that spreads from the face, upper aspect of trunk, and upper extremities to the lower extremities. However, there can be the development of pustules. DRESS is associated with a longer latent period of 2 to 6 weeks, compared with 1 to 2 days for AGEP. Mucous membrane and internal organ involvement are more common in DRESS as compared with AGEP.<sup>6</sup> SJS and TEN are characterized by epidermal sloughing, a positive Nikolsky sign, and mucous membrane involvement. It may be difficult to distinguish severe cases of AGEP,

**Table I.** Diagnostic score for acute generalized exanthematous pustulosis from EuroSCAR study<sup>40</sup>

Variable	Score
Morphology	
Pustules	
Typical	+2
Compatible with disease	+1
Insufficient	0
Erythema	
Typical	+2
Compatible with disease	+1
Insufficient	0
Distribution	
Typical	+2
Compatible with disease	+1
Insufficient	0
Course	
Mucous membrane involvement	
Yes	-2
No	0
Acute onset	
Yes	0
No	-2
Resolution within 15 d	
Yes	0
No	-2
Fever $\geq 38^{\circ}\text{C}$	
Yes	+1
No	0
Polymorphonuclear cells $\geq 7000$ cells/mm <sup>3</sup>	
Yes	+1
No	0
Histology	
Other disease	-10
Not representative	0
Exocytosis of polymorphonuclear cells	+1
Subcorneal and/or intraepidermal nonspongiform or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustules without papillary edema	+2
Spongiform subcorneal and/or intraepidermal pustules with papillary edema	+3

Score interpretation:  $\leq 0$  = no; 1-4 = possible; 5-7 = probable; 8-12 = definitive acute generalized exanthematous pustulosis. NOS, Not otherwise specified. Reprinted with permission.<sup>40</sup>

especially the rare cases with mucous membrane involvement, from SJS/TEN. However, histologic features of TEN include full-thickness epidermal necrosis with a lymphocytic infiltrate at the dermoepidermal junction.<sup>5</sup> The clinical features of Sweet syndrome include the abrupt onset of painful erythematous plaques on the face, neck, and arms.<sup>42</sup> Sweet syndrome may involve pustules and in rare cases include oral ulcers. The histologic

features of Sweet syndrome include edema in the papillary dermis, neutrophil infiltrate in the dermis, and lack of vasculitis (Table II).

## TREATMENT

The main treatment is removal of the causative drug, which leads to improvement in symptoms within several days. Moist dressings and antiseptic solutions are appropriate during the pustular phase to help prevent infection. Antibiotics should be avoided, unless a superinfection of the pustules occurs. Topical corticosteroids may be appropriate for treatment of pruritus and inflammation in prolonged cases. Treatment with potent topical corticosteroids has been correlated with decreased duration of hospitalization.<sup>43</sup> Patients have been treated with systemic corticosteroids; however, evidence that systemic corticosteroids reduce disease duration is unclear.<sup>44-46</sup>

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**Table II.** Characteristic findings of severe cutaneous drug reactions

	SJS/TEN	DRESS	AGEP
Onset of eruption	1-3 wk	2-6 wk	24-48 h
Duration of eruption, wk	1-3	Several	<1
Fever	+++	+++	+++
Cutaneous features	Bullae, mucocutaneous erosions	Morbilloform characterized by a diffuse, pruritic, macular exanthema	Nonfollicular, sterile pustules on an erythematous base with minimal mucous membrane involvement
Histology	Epidermal necrosis	Perivascular lymphocytic infiltrate	Intracorneal, subcorneal, and/or intraepidermal pustules
Visceral involvement	Tubular nephritis and tracheobronchial necrosis	Interstitial nephritis, pneumonitis, myocarditis, and thyroiditis	In up to 20% of cases
Neutrophils	↓	↑	↑↑↑
Eosinophils	—	↑↑↑	↑
Mortality, %	30-40	10	5

AGEP, Acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and system symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. Reprinted with permission.<sup>7</sup>

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