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REVIEW ARTICLE

Acute Generalized Exanthematous Pustulosis: Clinical Features, Differential Diagnosis, and Management

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Abstract

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute, severe cutaneous adverse reaction mainly attributed to drugs, although other triggers, including infections, vaccinations, ingestion of various substances, and spider bites, have also been described. AGEP is characterized by the development of edema and erythema followed by the eruption of multiple punctate, non-follicular, sterile pustules and subsequent desquamation. AGEP typically has a rapid onset and prompt resolution within a few weeks. The differential diagnoses for AGEP are broad and include infectious, inflammatory, and drug-induced etiologies. Diagnosis of AGEP depends on both clinical and histologic criteria, as cases of overlap with other disease processes have been reported. Management includes removal of the offending drug or treatment of the underlying cause, if necessary, and supportive care, as AGEP is a self-limited disease. This review aims to provide an overview and update on the epidemiology, pathogenesis, reported precipitating factors, differentials, diagnosis, and management of AGEP.

Key Points

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute, severe cutaneous adverse reaction mainly attributed to drugs, although other triggers have been described.

While the differential diagnosis list is broad, AGEP typically has a rapid onset and resolution within a few weeks, and management includes removal of the offending drug or treatment of underlying cause and supportive care

1 Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute, severe cutaneous adverse reaction attributed mainly to drugs. However, other triggers have also been described. Originally considered a variant of pustular psoriasis, AGEP was first described as its own separate condition by Baker and Ryan in 1968 [1, 2]. The name 'acute generalized exanthematous pustulosis' was then proposed by Beylot et al. in 1980 [3]. It is characterized by the development of edematous erythema, usually in large skin folds, followed by the eruption of multiple punctate, non-follicular, sterile pustules and subsequent typical desquamation [4]. The reaction usually resolves within 15 days, and the overall prognosis is good [5]. These lesions often occur in the intertriginous areas, which may help to differentiate AGEP from other diagnoses. Mucosal involvement is mild and occurs in approximately 20% of cases. The cutaneous manifestations are often accompanied by systemic symptoms, mainly fever and leukocytosis, and may be

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associated with hepatic, renal, or pulmonary involvement. The clinical course of AGEP is characterized by sudden onset followed by rapid resolution within days of discontinuation of the offending drug. There is a validated score from the EuroSCAR group for the diagnosis of AGEP [6]. Treatment includes withdrawal of the offending drug and supportive care, including topical steroids, antipyretics, and antihistamines. In more severe cases, systemic steroids may be used. The purpose of this review was to provide an overview of the epidemiology, pathogenesis, precipitating factors, diagnosis, and management of AGEP.

2 Literature Search Methods

A literature review of AGEP was performed by searching PubMed/MEDLINE between January 1960 and October 2022. International articles were included if available in English. Emphasis was placed on recent publications, with at least 50% of cited studies published within the last 5 years. Search terms were 'AGEP', 'acute generalized exanthematous pustulosis', and 'generalized pustulosis'. Articles were selected by two reviewers according to their relevance to the topic.

3 Epidemiology

AGEP is estimated to occur in one to five people per million per year [7, 8]. AGEP has been reported more frequently in women, with a mean age of 56 years [8, 9]. AGEP has been associated with increased body mass index; the mechanism may be related to upregulated pro-inflammatory cytokines secondary to obesity [10, 11]. Latency to drug-induced AGEP is a bimodal distribution as evidenced by Table 1. Of note, certain drugs have a higher epidemiological risk than others, these include pristinamycin, ampicillin, amoxicillin, quinolones, hydroxychloroquine, sulfonamides, terbinafine, and diltiazem [12].

4 Pathogenesis

Several pathways have been implicated in the pathogenesis of AGEP, all leading to increased interleukin (IL)-8 secretion and subsequent neutrophil migration and survival. Patch testing and in vitro assays have suggested that AGEP is a T-cell-mediated delayed-type hypersensitivity reaction to a specific drug or other trigger [4]. Specifically, after exposure to the offending agent, antigen-presenting cells (APCs) present the antigen using major histocompatibility complex molecules, leading to the activation of CD4+ and CD8+ T cells that become drug-specific. These activated T cells then proliferate and migrate into the dermis and epidermis. Using the perforin/granzyme B and Fas ligand pathways, these drug-specific CD8+ T cells induce apoptosis of keratinocytes within the epidermis, tissue destruction and epidermal vesicle formation [2]. In addition, activated T cells secrete IL-8, which is a chemoattractant for neutrophils and contributes to the neutrophil-rich nature of the pustules and peripheral neutrophilia seen in AGEP [13].

T-helper (Th) 1 cells also predominate in AGEP. Th1 cells are thought to increase secretion of interferon (IFN)-γ and granulocyte/macrophage colony-stimulating factor, both of which promote neutrophil survival. Th2 cells producing IL-5 may also play a role, particularly in patients with eosinophilia, as IL-5 is a potent eosinophil stimulator. In addition, Th17 cells are also thought to play a role, as IL-17 and IL-22 produced by these cells synergistically promote downstream IL-8 secretion [2, 13].

Mutations in the IL-36RN gene, which encodes the IL-36 receptor antagonist, have been reported to be more common in some patients diagnosed with both AGEP and pustular psoriasis than in unaffected individuals [13–16]. IL-36 is a proinflammatory cytokine secreted by macrophages and keratinocytes, and IL-36 receptors have been identified at high levels on the surface of APCs in the skin [13]. The IL-36 receptor antagonist typically blocks inflammatory cytokine signaling, namely IL-36α, IL-36β, and IL-36γ [13, 16]. The *IL36RN* gene is a small gene with six exons located on chromosome 2 at position q14 [17]. Dysregulation of this pathway results in increased IL-36 signaling, leading to increased production of IL-6, IL-8, IL-1α, and IL-1β. This increase in signaling is thought to predispose individuals to pustular eruptions [2]. A 2019 study showed that amoxicillin and letrozole specifically trigger IL-36γ cytokine production by sorted CD14+ peripheral blood macrophages via toll-like receptor 4 and by keratinocytes in patients who are positive for AGEP by patch test or lymphocyte transformation test (LTT). These IL-36 cytokines then induce IL-8 secretion in an IL-36-dependent manner [13]. This is in contrast to the hypothesis that T cells alone drive AGEP and suggests that AGEP may be driven, at least in part, by an innate response to drugs, possibly via pattern recognition receptors [13].

4.1 Drugs

A number of drugs have been reported in the literature to be associated with AGEP; these drugs are summarized below and their lag times are summarized in Table 1. Antibiotics are the most commonly implicated drug class in AGEP, including β-lactams, β-lactamase inhibitors, cephalosporins,

Table 1 Implicated triggers of AGEP and time to onset of symptoms from suspected exposure

Cause		Time to onset from suspected exposure	References
Drugs			
Antibiotics			
β-lactams	Amoxicillin, ampicillin, oxacillin, piperacillin-tazobactam, dicloxacillin, faropenem	2–15 days	[18–29]
β-lactamase inhibitors	Clavulanic acid, tazobactam	2–5 days	[20, 22, 26–28, 30]
Cephalosporins	Cefixime, ceftriaxone, cefotaxime, cefepime	0 days–1 month	[31–37]
Cyclic lipopeptides	Daptomycin	3–24 days	[44, 45, 47]
Fluoroquinolones	Ciprofloxacin, tosufloxacin	1–4 days	[39, 40]
Glycopeptides	Telavancin, vancomycin	1.5–5 days	[49, 50]
Lincosamides	Clindamycin	2–8 days	[4, 41, 43]
Macrolides	Azithromycin	7 days	[38]
Sulfonamides	Trimethoprim-sulfamethoxazole	8 days	[42]
Tetracyclines	Tigecycline	2 days	[48]
Other	Metronidazole, pristinamycin	2 days	[46, 51]
Antiviral			
	Ritonavir	4–10 days	[58]
	Acyclovir	1 day	[70]
	Remdesivir	1 month	[71]
	Favipiravir	7 days	[72]
Antifungal			
	Terbinafine	2 days–2 weeks	[73–78]
	Fluconazole	1 day	[79]
	Miconazole oral gel	2 days	[80]
	Nystatin	7 days	[81]
Antiparasitic			
	Praziquantel	1 day	[82]
	Benznidazole	6 weeks	[83]
Antimalarial			
	Hydroxychloroquine	4–122 days	[8, 53–68]
	Atovaquone-proguanil	3 weeks	[84]
Anticancer			
Chemotherapy	Bendamustine, docetaxel, gemcitabine, mycophenolate mofetil, paclitaxel	1 day–9 weeks, second cycle of chemotherapy	[85–92]
Targeted therapy	Cetuximab, erlotinib, rituximab, sorafenib, vismodegib	8 days–8 weeks	[93–98]
Immunotherapy	Pembrolizumab, ipilimumab, nivolumab, atezolizumab, interleukin-2	2 days–20 weeks	[99–104]
Anticoagulants			
DOACs	Apixaban	10 hours	[105]
NOACs	Enoxaparin	2 days	[106, 107]
Antiplatelet	Clopidogrel, ticagrelor	2–5 days	[108, 109]
Other drugs from various classes			
Anti-arrhythmics	Amiodarone, propafenone	2–10 days	[123, 124]
Anticonvulsants	Levetiracetam, valproic acid	5 days–8 weeks	[128, 129]
Antihypertensives	Diltiazem, hydroxyzine, ranolazine	2–12 days	[125–127]
Antipsychotics	Cariprazine, haloperidol, olanzapine, quetiapine	1–7 days	[130–133]
Diabetes therapy	Gliclazide, linagliptin	3–6 days	[110, 111]
NSAIDs	Celecoxib, ibuprofen, lornoxicam, piroxicam	0–4 days	[114–117]
Hormonal therapy	Letrozole, mifepristone	Hours–15 days	[92, 138, 139]

Table 1 (continued)

Cause		Time to onset from suspected exposure	References
Opioids	Codeine, dextromethorphan	1 day–2 weeks	[25, 134–137]
Topical agents	Mephenesin balm, topical diphenhydramine, transdermal ketoprofen, topical morphine	1–10 days	[119–122]
Other drugs	Alendronate	15 days	[140]
	Benzocaine	1 day	[126]
	Cannabidiol	2 days	[141]
	Dupilumab	2 days	[142]
	Finasteride	3 months	[143]
	Isotretinoin	5 days	[144]
	Methimazole	7 days	[145]
	Mianserin	7 days	[146]
	Midodrine	22 days	[147]
	Pantoprazole	4 days	[148]
	Paracetamol	4 days	[112, 113]
	Prednisolone	1 day	[118]
	Pseudoephedrine/fexofenadine	4 days	[149]
	Varenicline	10–11 days	[150]
Infections			
Bacterial	*Chlamydia pneumoniae, Mycoplasma pneumoniae*	Unknown[a]	[151, 152]
Fungal	Coccidiomycosis	3 days	[153]
Viral	COVID-19, Epstein–Barr virus, cytomegalovirus, parvovirus B19	COVID: 3 days after diagnosis–4 days after resolution Other unknown[a]	[23, 154–160]
Vaccinations			
COVID-19 (Moderna; first or second dose)		0 days–3 weeks	[161–164]
Influenza		1 day	[165]
Other causes			
Iatrogenic	Icodextrin, iodinated contrast, iron carboxymaltose infusions	1 day–2 weeks	[28, 167–172]
Dietary	Curcumin, oral blue dye, shiitake mushroom	1 day–1 month	[173–175]
Other	Spider bite	Immediately	[176–178]

AGEP acute generalized exanthematous pustulosis, *COVID-19* coronavirus disease 2019, *DOACs* direct oral anticoagulants, *NOACs* non-oral anticoagulants, *NSAIDs* non-steroidal anti-inflammatory drugs

[a]Skin findings were visible prior to serology confirming infection

macrolides, fluoroquinolones, sulfonamides, and clindamycin, among others [4, 18–51].

The β-lactams and β-lactamase inhibitors that have been reported in the literature include oxacillin, dicloxacillin, amoxicillin ± clavulanic acid, piperacillin-tazobactam, and faropenem [18–30]. Cephalosporins implicated in AGEP include cefixime, ceftriaxone, cefepime, and cefotaxime [31–37]. Azithromycin has been reported of the macrolide class [38]. Fluoroquinolones, including ciprofloxacin and tosufloxacin, have also been reported as associated with AGEP [39, 40]. Other antibiotics from various classes include clindamycin, tigecycline, telavancin, trimethoprim-sulfamethoxazole, vancomycin, daptomycin, metronidazole, and pristinamycin [4, 41–51].

Hydroxychloroquine is the next most frequently implicated drug reported after antibiotics as a whole, with 44 cases reported in a recent review [52]. Particularly in the era of the coronavirus disease 2019 (COVID-19) pandemic from 2020 to present, there have been increased reports of hydroxychloroquine-induced AGEP, which may be secondary to increased use of the drug [8, 53–68]. Of note, hydroxychloroquine-induced AGEP typically has a delayed onset compared with other drugs due to its long half-life of 40–50 days [69].

Other antimicrobials implicated in the pathogenesis of AGEP include antifungals, namely fluconazole, miconazole oral gel, nystatin, and terbinafine; antivirals, including acyclovir, favipiravir, remdesivir, and ritonavir; antiparasitic

drugs, namely benznidazole and praziquantel; and other antimalarials, including atovaquone/proguanil [58, 70–84].

Anticancer therapies have also been associated with AGEP, including chemotherapy, such as bendamustine, docetaxel, gemcitabine, mycophenolate mofetil, and paclitaxel; targeted therapy, including cetuximab, erlotinib, rituximab, sorafenib, and vismodegib; and immunotherapy, such as pembrolizumab, ipilimumab, nivolumab, atezolizumab, and IL-2 [85–104].

Direct oral anticoagulants, including apixaban and dabigatran, as well as non-oral anticoagulants, namely enoxaparin, have been reported a few times in the literature [105–109]. Diabetes medications, including DPP-4 inhibitors (linagliptin) and sulfonylureas (gliclazide), have been reported as implicated in AGEP [110, 111].

A number of other drugs have also been reported in the literature, including analgesics and anti-inflammatories, such as paracetamol, celecoxib, ibuprofen, piroxicam, prednisolone, topical mephenesin balm, transdermal ketoprofen, and topical morphine [112–122].

Antiarrhythmics, such as amiodarone and propafenone, and antihypertensives, including diltiazem, hydralazine, and ranolazine have also been reported [123–127]. Anticonvulsants, including valproic acid and levetiracetam, and antipsychotics, including cariprazine, haloperidol, olanzapine, and quetiapine, have been implicated in AGEP, as have opioids, including codeine and dextromethorphan [25, 128–137]. Hormonal therapies, including letrozole and mifepristone have been implicated in AGEP [92, 138, 139]. Other drugs such as alendronate, benzocaine, cannabidiol, dupilumab, finasteride, isotretinoin, methimazole, mianserin, midodrine, pantoprazole, pseudoephedrine/fexofenadine, and varenicline have also been reported [126, 140–150].

4.2 Infections

Multiple infections have been reported in relation to AGEP onset. Reports of AGEP after *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, coccidiomycosis, COVID-19, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and parvovirus B19 have been identified [23, 151–160]. As these causative agents cannot be removed, treatment of underlying infection and supportive care until resolution are the mainstay of management. Given that AGEP occurs in patients with underlying infectious disease and may also occur in patients who take certain antibiotics, the correlation must be noted. It is possible that patients with underlying infectious disease may be more susceptible to developing AGEP. It may also be possible that patients with underlying infectious disease develop AGEP as a sequelae of the pharmacologic treatment used to treat the infection. This could also explain why prompt resolution occurs within a few weeks in AGEP.

4.3 Vaccinations

There have been reports of AGEP occurring after influenza vaccination and spikevax COVID-19 vaccination (Moderna) [161–165]. The pathogenesis may be due to the cytokine storm-like global immune activation that can occur after COVID-19 infection or vaccination [161]. While this is not a reason to avoid vaccination, it is important to be aware of this potential adverse event in order to improve prompt diagnosis, initiate treatment, and minimize morbidity and mortality. Of note, given the high frequency of influenza vaccination and mRNA COVID-19 vaccination (Moderna) internationally, it must be stated that the epidemiological risk of developing AGEP remains very low. There is also no proven causation between vaccination and AGEP, only clinical correlates, and thus it also may be true that there are overlapping phenotypes and/or misclassifications of neutrophilic pustulosis as AGEP [166]. Vaccinations cannot be discontinued like offending drugs; in these cases, supportive care is most important.

4.4 Other

Non-drug or non-infectious causes of AGEP include a variety of etiologies. Iatrogenic triggers include icodextrin, iodinated contrast, and iron carboxymaltose infusions [28, 167–172]. Dietary triggers include curcumin, oral blue dye, and shiitake mushrooms. Spider bites have also been reported to trigger AGEP [173–178]. Specifically, envenomation by the brown recluse spider *Loxosceles reclusa* has been reported in the literature as a trigger for AGEP [176–178].

5 Clinical Presentation

AGEP typically presents within 24–48 h of ingestion of the offending drug, with a median time of 24 h for antibiotics in particular. However, some drugs have been shown to have a lag time of up to 10–22 days; therefore, this is not a defining feature [2, 8]. Prodromal signs include fever (>38°C) and generalized malaise with leukocytosis, particularly neutrophilia, with eosinophilia in up to 30% of patients [2]. This is accompanied by an edematous erythema and a pruritic pustular eruption that favors the trunk and intertriginous areas, often sparing the mucous membranes, followed by desquamation of the affected areas. The pustules are sterile, non-follicular, and numerous (Fig. 1). Mucosal involvement occurs in approximately 20% of cases [5]. When mucosal involvement occurs, the rash is usually limited to a single site such as the lips or buccal mucosa [9]. Atypical presentations of AGEP include eruption of atypical targetoid lesions or bullae in response to an inciting agent [179].

Systemic involvement is considered to be any organ dysfunction that occurs with cutaneous features that cannot be attributed to any other cause or disease. Studies have shown that 17–20% of AGEP cases have internal organ involvement, most often hepatic, renal, or pulmonary disease [2, 4, 180].

Hepatic findings involve enzyme elevation in either a hepatocellular pattern (elevated aspartate aminotransferase and alanine aminotransferase to twice greater than normal) or a cholestatic pattern (elevated alkaline phosphatase and γ-glutamyl transferase) [7]. Abdominal ultrasound findings may show steatosis or hepatomegaly, both of which are nonspecific. Renal findings may include creatinine >1.5 times baseline, suggestive of severe acute kidney injury [7]. Pulmonary findings may include pleural effusions, hypoxemia, and increased oxygen requirements [2, 180]. Other nonspecific signs of systemic involvement include elevated absolute neutrophil count and C-reactive protein [9, 180]. Systemic symptoms typically resolve with discontinuation of the causative drug, treatment of the underlying condition, and supportive care. AGEP cases accompanied by systemic symptoms tend to cause greater morbidity and mortality compared with AGEP cases with only cutaneous features [2].

Acute localized exanthematous pustulosis (ALEP) is a subtype of AGEP in which lesions are localized to one or few areas of the skin [181]. The face is the most frequently affected area followed by the trunk and upper extremities. The clinical features and pattern of lesion evolution from erythema to pustules to desquamation is the same in ALEP as it is in AGEP. The inciting triggers for ALEP have also been the same as those reported in AGEP, with drugs, specifically antibiotics, being the most common trigger. Compared with AGEP, ALEP is less likely to have systemic involvement; ALEP is typically accompanied by normal laboratory tests without changes to renal or liver function [182]. However, a few ALEP cases do report concurrent leukocytosis [183, 184]. Pathogenesis of ALEP has not been investigated; the majority of available research is case reports and case series [20, 182].

6 Diagnosis

Diagnosis of AGEP depends on clinical and histologic criteria. An AGEP score was proposed by the EuroSCAR group based on morphology, clinical course, and histology [6]. This scoring tool classifies patients with suspected AGEP as having definite, probable, possible, or no AGEP (Table 2). A drug patch test can be used to identify the cause of AGEP [8]. It is recommended that these tests are generally performed no sooner than 4 weeks after the resolution of AGEP but within 1 year after the adverse reaction [185]. The sensitivity of patch testing for AGEP is estimated to be 50–58% [185, 186]. As such, when patch tests

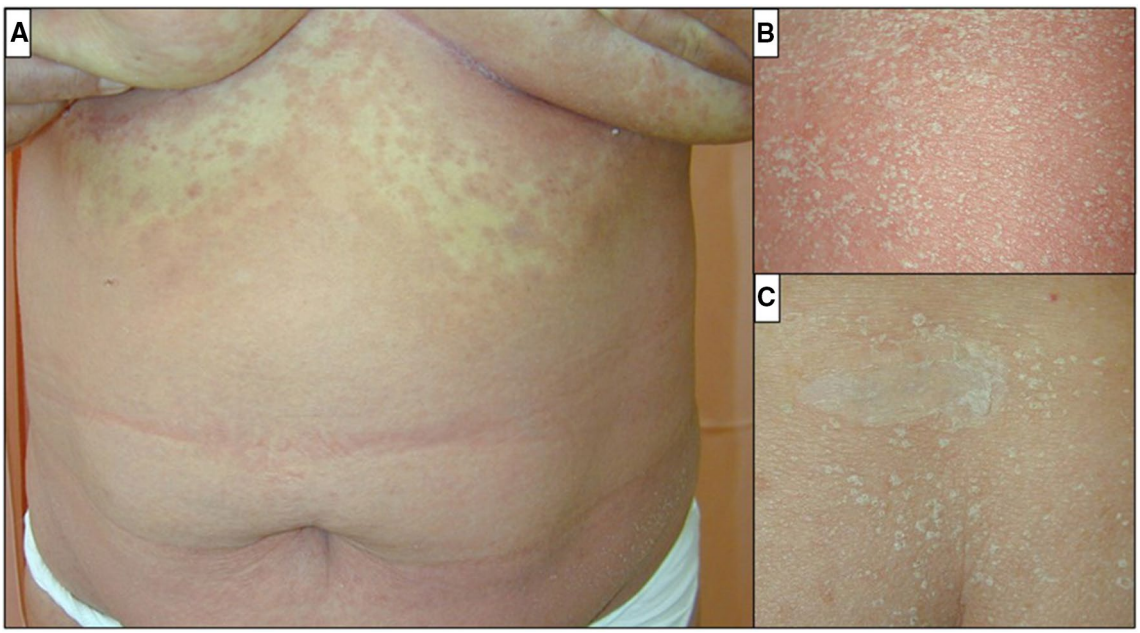

Fig. 1 Clinical presentation and progression of acute generalized exanthematous pustulosis in a patient 3 days after oral clindamycin initiation: (**a**) 3 days of intertriginous erythema followed by (**b**) pustules overlying the erythema for 2–3 days, followed by (**c**) subsequent desquamation of the affected skin approximately 1 week after appearance of the rash

are negative but clinical suspicion remains high, intradermal tests or prick tests may be utilized next [185, 186]. The recommendations vary between the United States and Europe, with European guidelines considering prick tests to be safer than intradermal tests [186]. However, in more recent studies, prick tests have been suggested to have limited value for AGEP, with intradermal tests considered 'potentially useful' but must be performed in a hospital setting and are contraindicated when involving 'drugs that are highly suspected' [185]. An LTT may also be used to assist in AGEP diagnosis. LTT may demonstrate significant lymphocyte stimulation toward medications that induced AGEP, despite negative skin testing [187].

Table 2 Diagnostic scoring system for AGEP, adapted from the EuroSCAR study group [6]

Characteristic	Score
Morphology	
Pustules	
Typical	+2
Compatible with disease	+1
Insufficient	+0
Erythema	
Typical	+2
Compatible with disease	+1
Insufficient	+0
Distribution/pattern	
Typical	+2
Compatible with disease	+1
Insufficient	+0
Post-pustular desquamation	
Yes	+1
No/insufficient	+0
Course	
Mucosal involvement	
Yes	− 2
No	+0
Acute onset within 10 days of exposure	
Yes	+0
No	− 2
Resolution within 15 days	
Yes	+0
No	− 4
Fever (temperature ≥ 38°C)	
Yes	+1
No	+0
PMNs > 7000/mm^3	
Yes	+1
No	+0
Histology	
Consistent with other disease	− 10
Not representative/no histology	+0
Exocytosis of PMNs	+1
Subcorneal and/or intraepidermal non-spongiform or NOS pustule(s) with papillary edema OR subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary edema	+2
Spongiform subcorneal and/or intraepidermal pustule(s) with papillary edema	+3

Score interpretation: ≤0 = not AGEP; 1–4 = possible AGEP; 5–7 = probable AGEP; 8–12 = definitive AGEP

AGEP acute generalized exanthematous pustulosis, *NOS* not otherwise specified, *PMNs* polymorphonuclear leukocytes

7 Histopathologic Findings

Histologic features of AGEP are characterized by intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema and both neutrophilic and eosinophilic perivascular and interstitial infiltrate [186, 188]. The intraepidermal pustules tend to be primarily in the upper epidermis and may be contiguous with subcorneal pustules. Spongiosis may also be seen, particularly in the intracorneal and subcorneal pustules, and necrotic keratinocytes are often also present [186]. Histologic findings of a patient who developed AGEP are shown in Fig. 2.

8 Differential Diagnosis

The differential diagnosis of AGEP is quite broad and includes mainly infectious diseases, inflammatory papulosquamous diseases, and adverse drug reactions (summarized in Table 3). Infectious diseases include bacterial folliculitis, cutaneous candidiasis, and herpes simplex virus (HSV). Non-infectious inflammatory papulosquamous differentials mainly include pustular psoriasis, immunoglobulin (Ig) A pemphigus, and subcorneal pustular dermatosis. Adverse drug reactions include drug reaction with eosinophilia and systemic symptoms (DReSS), Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug-induced eosinophilic pustular folliculitis (Ofuji disease). It is important to biopsy cutaneous lesions for standard histology and to consider perilesional biopsy for direct immunofluorescence (DIF). Due to the important differential diagnosis of infectious etiologies, it is always advisable to obtain the following from a pustule: direct smear, culture for gram stain, and consider culture for candida and polymerase chain reaction (PCR) for viral disease such as herpes based on clinical manifestations.

There are some clinical clues to differentiate AGEP from other conditions. Bacterial folliculitis is distinguished by the follicular pattern of bacterially infected pustules compared with the nonfollicular distribution of sterile pustules in AGEP. Direct Gram stain and bacterial culture from pustules are an important part of the differentiation. Histopathology may also be helpful [189]. Cutaneous candidiasis typically presents with erythematous papules, plaques, and pustules, usually in intertriginous areas and often with skin maceration. Pustules typically develop at the margins of plaques, and satellite pustules may also develop. Histopathology often shows micropustules beneath the stratum corneum coalescing into large pustules [190]. Neutrophils may penetrate the underlying spongiotic stratum corneum and the dermis is often edematous with a perivascular and interstitial infiltrate composed mainly of neutrophils. Periodic acid-Schiff (PAS) staining may reveal the organism. Fungal culture and potassium hydroxide (KOH) preparation to assess for pseudohyphae and budding yeast may aid in diagnosis. Patients who are immunocompromised, overweight/obese, and have poor hygiene, nutritional deficiencies such as iron deficiency, and/or endocrine disorders such as diabetes mellitus are more likely to develop cutaneous candidiasis [190, 191]. Herpetic viral infections may mimic AGEP due to the clinical presentation of vesicles and pustules on an erythematous base. However, herpes virus is more likely to be localized and herpes zoster is classically distributed in a dermatomal pattern. Histology of HSV lesions shows ballooning degeneration of keratinocytes and multinucleated giant cells. In addition, Tzanck smear and PCR can aid in differentiation [192]. No cases of AGEP and bacterial

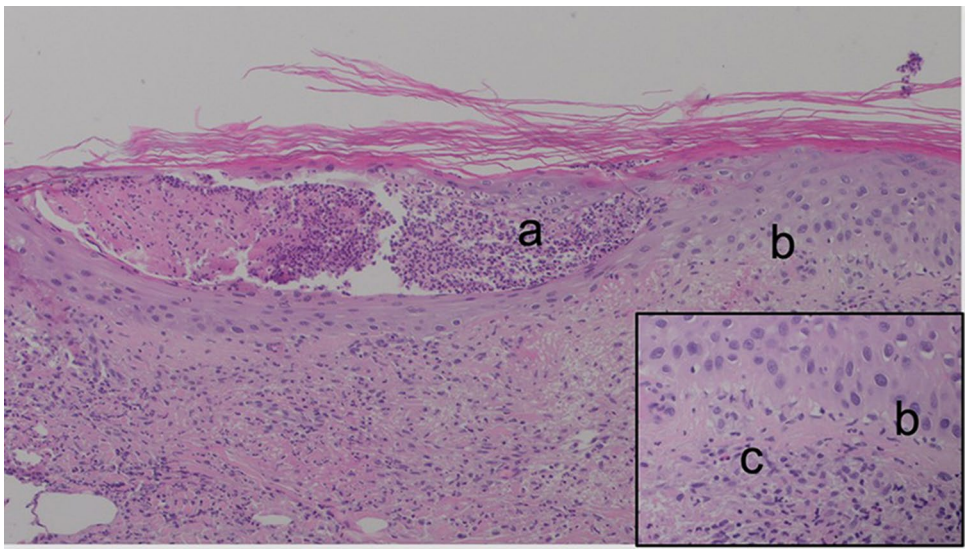

Fig. 2 Representative HE histology of AGEP depicting (**a**) a subcorneal neutrophilic pustule, (**b**) vacuolization of basal keratinocytes in the adjacent epidermis, accompanied by (**c**) a mixed infiltrate in the upper dermis consisting of lymphocytes, histiocytes, neutrophils and admixed eosinophils. Magnification: 40×, inset 100×. *AGEP* acute generalized exanthematous pustulosis, *HE* hematoxylin and eosin

Table 3 Common differential diagnoses of AGEP

	Clinical and cutaneous features	Histology	DIF	Systemic symptoms	Laboratory tests	Typical patient population	Overlap with AGEP
Bacterial folliculitis [189]	Follicular pattern, often in hair-bearing and intertriginous areas	Neutrophilic invasion of hair follicle and perifollicular tissue, primarily where the sebaceous glands and ducts meet follicle	Not indicated	None	Direct smear with gram stain and bacterial culture	Patients with a history of diabetes, obesity, prolonged antibiotic use, or immune-compromise, or those who shave frequently	No cases reported
Cutaneous candidiasis [190, 191]	Red papules, plaques, and pustules mostly in intertriginous areas often with skin maceration; characteristically with pustules on the edge of the plaques and satellite pustules may develop	Micropustules beneath the stratum corneum coalesce into large pustules; neutrophils permeate through the underlying spongiotic stratum corneum; dermis is edematous with perivascular and interstitial infiltrate composed mostly of neutrophils. PAS may reveal the organism	Not indicated	None	Fungal culture and KOH prep for pseudohyphae and budding yeast	Immunocompromised, overweight/obese, patients with nutritional deficiencies such as iron deficiency, and endocrine diseases such as diabetes mellitus, patients with poor hygiene	No reported cases
Herpes simplex virus [225]	Vesicles and pustules clustered on erythematous base often near the mouth, genitals, or buttocks	Ballooning degeneration of keratinocytes and multinucleated giant cells	Not indicated	Localized pain, tenderness, burning, or tingling prior to onset, and may be accompanied by a viral prodrome (malaise, fevers, tender LAD)	PCR, Tzanck smear, serology	Varied, increased risk in immune-compromised patients	No cases reported
Pustular psoriasis (including pustular psoriasis of pregnancy/impetigo herpetiformis) [179, 193–197, 199]	Sterile, nonfollicular pustules overlaying scaly plaques	Intraepidermal pustules with neutrophilic infiltrates, spongiosis, papillomatosis, acanthosis, and micro-abscesses	Negative	History of psoriasis or psoriatic arthritis, constitutional symptoms (malaise, fatigue, fever), oral, ocular, bone, and/or joint involvement	Histology	Patients with a history of psoriasis vulgaris or psoriatic arthritis	AGEP and pustular psoriasis overlap after ceftriaxone therapy
IgA pemphigus [200]	Pruritic subacute eruption of flaccid pustules on an erythematous base in flexural areas	Subcorneal blisters with neutrophils and loss of cohesion between keratinocytes	DIF of perilesional skin: IgA autoantibodies on keratinocyte cell surfaces	Rarely mucous membrane involvement	Histology, DIF, IIF, ELISA, immunoblotting	Middle age or elderly individuals	No cases reported

Table 3 (continued)

	Clinical and cutaneous features	Histology	DIF	Systemic symptoms	Laboratory tests	Typical patient population	Overlap with AGEP
Subcorneal pustular dermatosis (Sneddon–Wilkinson disease) [201, 202]	Flaccid sterile pustules on normal or mildly erythematous skin, often on the trunk, flexural surfaces, and intertriginous areas	Subcorneal blisters with neutrophils and eosinophils that classically sit above an undisturbed epidermis with minimal spongiosis	Typically negative; few reports of positive DIF with epidermal intercellular deposits of IgA	None	Histology, DIF, IIF	Middle age or elderly women	No cases reported
Eosinophilic pustular folliculitis (Ofuji disease) [5, 211, 214–216]	Pruritic follicular papules and pustules in areas above the trunk	Spongiosis and perifollicular lymphohistiocytic infiltrate, ± micro-abscesses of eosinophils	Not indicated	None	HIV serology	Patients with HIV, patients receiving chemotherapy, third decade of life, Japanese women	No cases reported
DReSS [164, 204, 207]	Polymorphic rash that may include pustules and vesicles, commonly facial edema, and possible mucosal involvement, classically long lag period (4–8 weeks)	Varied, may include basal squamatization, dermal red blood cell extravasation, or interface inflammation	Not indicated	Systemic involvement is prominent, including constitutional symptoms (fever, malaise) and various organs (liver, kidney, lung, brain, muscle/heart, pancreas, etc.)	CBC with diff and direct smear (atypical lymphocytes, eosinophilia), ESR, CRP, CMP (LFTs, creatinine), lipase, amylase, CK, troponin, urinary protein and cells, PCR for HHV6, HHV7, CMV, EBV	Patients with genetic predisposition and possible concurrent viral disease	Many cases, for example AGEP and DReSS, overlap in a patient after COVID-19 vaccine and in patients receiving vemurafenib
SJS/TEN [208, 210, 226]	Flu-like prodrome followed by cutaneous involvement with erythematous dusky purpuric macules (atypical target lesions), +Nikolsky sign, and mucosal involvement with ocular, oral, and genital lesions	Full-thickness keratinocyte necrosis	Negative	Constitutional symptoms (weakness, pain, high fever, malaise, headache); internal organ involvement mainly of the respiratory and GI tracts but any other systems can be involved	CBC with diff (look for leukocytosis), ESR, CRP, CMP (hyponatremia, creatinine, LFTs), ECG	Varied; genetic predisposition, more common in patients with HIV	Many cases, for example AGEP and SJS, overlap in a patient treated with ceftriaxone, metronidazole, and vancomycin simultaneously

AGEP acute generalized exanthematous pustulosis, *DReSS* drug reaction with eosinophilia and systemic symptoms, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis, *DIF* direct immunofluorescence, *IIF* indirect immunofluorescence, *PAS* periodic acid-Schiff, *KOH* potassium hydroxide, *LAD* lymphadenopathy, *IgA* immunoglobulin A, *CBC with diff* complete blood count with differential, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *CMP* comprehensive metabolic panel, *LFT* liver function tests, *CK* creatinine kinase, *PCR* polymerase chain reaction, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *GI* gastrointestinal, *ECG* electrocardiogram, *HIV* human immunodeficiency virus, *ELISA* enzyme-linked immunosorbent assay

folliculitis, cutaneous candidiasis, or HSV overlap have been reported.

Differentiating between AGEP and pustular psoriasis, including the subtypes of acute, annular, and pustular psoriasis of pregnancy (impetigo herpetiformis), is challenging. However, it is important to differentiate the diagnoses in order to determine the most effective treatment. Clinically, the difference is usually very subtle and both conditions present with sterile, nonfollicular pustules. Pustular psoriasis may be associated with constitutional symptoms (malaise, fatigue, fever) and oral, ocular, bone, and/or joint involvement [193, 194]. Genetically, both diseases were found to have mutations in IL-36RN [13, 14]. The following may assist in differentiation: (1) pustular psoriasis lesions usually overlay scaly plaques [195]; (2) patients with pustular psoriasis often have a characteristic history of plaque psoriasis; and (3) have differences in comorbidities, such as psoriatic arthritis. In addition, Shalom et al. [196] found that hypertension, diabetes mellitus, and dyslipidemia were associated with pustular psoriasis and drug-induced psoriasis at significantly higher rates than with AGEP. Other differences include (4) the histopathology of AGEP is more likely to demonstrate neutrophilic and eosinophilic infiltrates and necrotic keratinocytes, as opposed to exclusively neutrophilic infiltrates in pustular psoriasis [196, 197]. In addition, in pustular psoriasis, spongiosis is more prominent, with macro-pustules at a higher epidermal level than in AGEP [188]. Lastly, pustular psoriasis often has papillomatosis and acanthosis, as well as micro-abscesses, which are absent in AGEP [179]. However, even with these reported differences, the histological differentiation is challenging [188, 196, 198]. Vyas et al. [198] found that the presence of CD123, a marker for plasmacytoid dendritic cells, and MxA proteins in dermal inflammatory infiltrate are helpful in distinguishing pustular psoriasis from AGEP. CD161 positivity also supports a diagnosis of pustular psoriasis [197].

There are reports of overlap between AGEP and pustular psoriasis in which a distinction cannot be made [198, 199]. For example, a case of overlap between AGEP and pustular psoriasis in response to ceftriaxone has been reported, in which a patient with psoriasis vulgaris developed an isolated pustular eruption after use of the antibiotic. However, it was not clear whether this was a case of AGEP in a patient with a history of psoriasis or an acute exacerbation of pustular psoriasis [199].

IgA pemphigus typically presents with a subacute eruption of flaccid pustules on an erythematous base. The pustules often rupture to form a painful and pruritic crust over the plaque. Similar to AGEP, the cutaneous eruptions are often located in flexural areas. However, unlike AGEP, IgA pemphigus is very rarely associated with systemic symptoms such as fever or mucosal involvement. IgA pemphigus is differentiated by histology and most commonly by DIF of the perilesional skin. Enzyme-linked immunosorbent assay, indirect immunofluorescence (IIF), or immunoblotting may also be used. IgA pemphigus histology usually shows subcorneal vesicles with neutrophilic infiltration and occasional loss of adhesions between keratinocytes. DIF is characterized by the presence of IgA autoantibodies in the epidermis, particularly on the surfaces of keratinocytes. [197, 200]. IgA pemphigus has been associated with monoclonal IgA gammopathy, human immunodeficiency virus infection, Sjogren disease, rheumatoid arthritis, and Crohn's disease. IgA pemphigus presents more often in middle age or elderly individuals. There is no particular patient population in terms of race or sex with which IgA pemphigus is closely associated [200]. There have been no reported cases of concurrent or overlapping IgA pemphigus and AGEP.

Subcorneal pustular dermatosis (SPD), also known as Sneddon–Wilkinson disease, is a rare, benign, relapsing neutrophilic dermatosis that presents with flaccid sterile pustules on normal or mildly erythematous skin, often on the trunk, flexural surfaces, and intertriginous areas [201, 202]. These may develop into characteristic 'half and half' vesicles, with pus accumulation in the lower half and clear fluid overlying it. These pustules may be isolated or grouped; when grouped they tend to coalesce into annular, circumferential, or serpiginous patterns. Pruritus is not a prominent feature, although it may be present. The course of the disease is often cyclic. There is typically no fever or other systemic symptoms [201]. SPD presents histologically, similarly to SPD-type IgA pemphigus and annular pustular psoriasis with subcorneal neutrophilic and eosinophilic pustules [201, 202]. However, the pustules in SPD are exclusively subcorneal and classically sit above an undisturbed epidermis with minimal spongiosis, contrary to pustular psoriasis, IgA pemphigus, and AGEP [201]. DIF is classically negative, although there are reports of epidermal intercellular deposition of IgA. Approximately half of cases with positive DIF also have positive IIF for circulating autoantibodies. SPD often occurs in association with various neoplastic, immunological, and inflammatory conditions, including IgA or IgG monoclonal gammopathies, lymphoproliferative disorders, especially multiple myeloma, B-cell lymphoma, systemic lupus erythematosus, rheumatoid arthritis, hyperthyroidism, Crohn's disease, and pyoderma gangrenosum. SPD is more common in middle-aged and older women. No particular ethnic or racial predominance has been reported [201, 202]. There have been no reported cases of SPD and AGEP overlap.

Adverse drug reactions, such as DReSS, SJS/TEN, and Ofuji disease need to be differentiated from AGEP. DReSS and AGEP both may display clinical features of fever and edematous erythema. DReSS is more likely to have mucosal involvement (50%) compared with AGEP (20%). DReSS is also more likely to have systemic involvement

(91%) compared with AGEP (17%) [203]. Systemic features of DReSS may include constitutional symptoms (fever, malaise) and systemic organ involvement in the liver, kidney, lung, brain, muscle/heart, or pancreas [204]. Therefore, it is advised to consider ordering various laboratory tests that may include the following: complete blood count with differential including search for atypical lymphocytes and eosinophilia, inflammatory markers, PCR for HHV6, HHV7, CMV, EBV, liver function tests, pancreatic enzymes, serum creatinine, urinary protein and cells, creatine kinase, and troponin [205].

Although DReSS may manifest with pustules and vesicles, similar to AGEP, the cutaneous features are more commonly morbilliform and polymorphic with accompanying facial edema and possible mucosal involvement. DReSS has a classically long lag period of 4–8 weeks. Significant eosinophilia is also more common in DReSS (over 50% of cases) compared with the mild eosinophilia that has been reported in about one-third of AGEP cases [203]. DReSS is a spectrum; mild cases demonstrate fewer systemic features and symptoms than major cases. The distinction between DReSS minor and DReSS major was recently conducted. DReSS minor, compared with DReSS major, had lower rates of facial edema, lesser degrees of elevated liver enzymes, and required shorter courses of immunosuppression [206]. Minor forms of DReSS may be more challenging to differentiate from AGEP. It is important to note that there have been cases of DReSS and AGEP overlap reported, for example in a patient receiving vemurafenib [207].

SJS/TEN and AGEP are both immune-mediated reactions, most often triggered by drugs; it is important to differentiate the two to rule out SJS/TEN, a disorder that is classically more severe than AGEP [179]. SJS/TEN typically presents with a flu-like prodrome followed by cutaneous involvement with erythematous dusky purpuric macules (atypical target lesions), a positive Nikolsky sign, and mucosal involvement with ocular, oral, and genital lesions [208]. Mucosal involvement is much less common in AGEP. If there is skin sloughing in AGEP, the etiology is due to pustule coalescence, unlike SJS/TEN where sloughing is due to epidermal necrosis and detachment. The definitive way to differentiate AGEP from SJS/TEN is by skin biopsy. Histopathology of AGEP will show subcorneal or intraepidermal neutrophilic pustules, whereas SJS/TEN will show full thickness keratinocyte necrosis [179, 209]. Both SJS/TEN and AGEP are immediately treated with discontinuation of the inciting drug or trigger [210]. A few cases of 'TEN-AGEP' overlap have been reported with bullae, mucosal involvement, and diffuse exfoliation mimicking SJS/TEN but with AGEP features on histology [179, 210]. Of note, drugs that induce AGEP are more likely to produce a positive patch test result compared with those involved in SJS/TEN [98].

Eosinophilic pustular folliculitis (Ofuji disease) can be differentiated from AGEP on the basis of clinical features and histological findings. Three subtypes of Ofuji disease have been described, including classical, immunosuppression-associated (most commonly HIV-associated), and infantile. In addition, cases of drug-induced Ofuji disease have been reported [211–213]. Most cases of drug-induced Ofuji disease have been triggered by chemotherapies such as cyclophosphamide, methotrexate, and 5-fluorouracil [5, 214]. The clinical presentation typically begins with pruritic follicular papules and pustules in areas over the trunk, such as the face, scalp, and arms. Histologically, Ofuji disease is often characterized by spongiosis and a perifollicular lymphohistiocytic infiltrate. There may be micro-abscesses of eosinophils within the follicular epithelium [5, 215]. Ofuji disease is classically not accompanied by any systemic symptoms; however, peripheral eosinophilia is a common finding [216]. Ofuji disease often recurs or is chronic, most commonly in patients with HIV or individuals aged in their 30s and is most well-characterized in Japanese women [211–213, 216]. There have been no reported cases of concurrent or overlapping Ofuji disease and AGEP.

9 Treatment

The mainstay of treatment for AGEP is withdrawal of the offending drug. In cases caused by infection or other triggers rather than a drug, treatment of the underlying cause is an important part of management. Otherwise, treatment is primarily symptomatic/supportive, as AGEP is usually self-limited. Supportive treatment may include topical steroids, antipyretics, and antihistamines [5, 217]. In severe cases, oral corticosteroids may be used and have been reported to be associated with reduction in length of hospital stay and morbidity [7]. In rare cases, AGEP was reported to be induced by oral corticosteroids. For example, a case of AGEP induced by prednisolone confirmed by patch testing was reported [118]. In such cases, all systemic steroid therapy is not necessarily contraindicated, as, in this report, the patient was able to tolerate methylprednisolone without recurrence of rash [118]. Cyclosporine is another option for severe AGEP with similar efficacy to oral corticosteroids that may be used in steroid-refractory cases or in patients with contraindications to steroid therapy [218]. Secukinumab and infliximab have also been successfully used to treat refractory cases that are not responsive to drug discontinuation, supportive care, or steroids [219, 220]. Due to the immunologic nature of AGEP, it is likely that other biologic medications targeting the aforementioned IL pathways can be utilized; however, further study is needed to determine the necessity, safety, dosing, and outcomes. The

healing process is characterized by cutaneous desquamation, for which topical emollients are recommended [221].

10 Clinical Prognosis and Long-Term Outcomes

Upon discontinuation of the causative agent, rapid resolution of symptoms, including the cutaneous features, typically occurs within a few days to 2 weeks [186]. Based on the diagnostic criteria for AGEP (Table 2), lack of resolution within 15 days reduces 4 points from the score, which decreases the likelihood of AGEP diagnosis and reflects the importance of this feature [6]. As AGEP resolves, there are typically collarettes of desquamation over the affected areas. Mortality in AGEP is less than 5%, and in cases where death occurs, it is usually due to multiple organ dysfunction, disseminated intravascular coagulation, or nosocomial infection rather than the cutaneous findings [2]. Those at highest risk of death are individuals with multiple comorbidities and more severe, diffuse cutaneous and mucous membrane involvement. More recent publications have suggested that death events in patients with AGEP may be unrelated to AGEP [52, 222]. In order to accurately assess AGEP-associated mortality, more research is needed to relate death events to follow-up periods, severity, treatment, and comorbidities. AGEP may, rarely, be followed by long-term complications in the event of multiorgan involvement, such as kidney damage, but this is rare and atypical and may resolve with the use of systemic corticosteroids [223]. It is important to note that AGEP can recur after reintroduction of the causative drug or trigger [23, 224].

11 Limitations

The main limitation of this review is that the AGEP literature consists mainly of case reports and research letters with retrospective data. In addition, in the absence of double-blind, placebo-controlled, randomized control trials, available treatment recommendations are largely based on clinical opinion. Limited data are available on the safety and sensitivity of patch, prick, and intradermal tests for diagnosis. In addition, different presentations of the eruption in skin of color may affect the clinical manifestations, making it difficult to characterize on a global level. Finally, this summary is not a systematic review, which limits the degree of objectivity. However, care has been taken to present a variety of different perspectives on the topics that are hotly debated in AGEP.

12 Conclusions

AGEP, first described in 1968 and later defined in 1980, continues to be studied. The aim of this review was to present the most recent information on the triggers, pathogenesis, clinical features, diagnosis, prognosis, and management of AGEP. Although significant progress has been made, more studies are needed to further characterize AGEP. In addition, literature is needed to educate clinicians in all settings to promote awareness of AGEP, as this would be beneficial to improve diagnostic accuracy and prompt management, particularly due to the rarity of the disease and the overlap between the clinical features of AGEP and other severe cutaneous eruptions.

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