Hindawi
Dermatologic Therapy
Volume 2024, Article ID 3885057, 7 pages
https://doi.org/10.1155/2024/3885057

Research Article

Clinical Characteristics, Treatment, and Prognosis of Amoxicillin-Induced AGEP/ALEP

Haibo Lei,[1,2] **Zhiqiang Fan**,[3] **Yang He**,[3] **Wei Sun**,[4] **Zuojun Li**,[4] **and Chunjiang Wang**[2,4]

[1]*Department of Clinical Pharmacy, Xiangtan Central Hospital, Xiangtan, Hunan 411100, China*
[2]*College of Pharmacy, Changsha Medical University, Changsha, Hunan 410219, China*
[3]*Department of Pharmacy, The First Hospital of Hunan University of Chinese Medicine, Changsha, Hunan 410007, China*
[4]*Department of Pharmacy, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, China*

Correspondence should be addressed to Chunjiang Wang; wongcj@csu.edu.cn

Received 1 May 2023; Revised 15 December 2023; Accepted 8 January 2024; Published 13 January 2024

Academic Editor: Xiaoming Liu

Background. Amoxicillin was associated with acute generalized exanthematous pustulosis (AGEP), and the clinical characteristics were not clear. The purpose of this study was to explore the clinical characteristics of amoxicillin-induced AGEP and to provide a basis for prevention and treatment. *Methods*. Case reports and case series of amoxicillin-induced AGEP were collected for retrospective analysis by searching the Chinese and English databases from inception to January 31, 2023. *Results*. A total of 46 patients were included with a median age of 40 years (range 1.4, 87). The onset time of AGEP ranged from 6 hours to 28 days, with a median of 2.5 days. Fever occurred in 32 patients (69.6%), and pruritus occurred in 13 patients (28.3%). Ten patients (21.7%) had mucous membrane involvement and systemic involvement, respectively. Twenty-two patients had elevated neutrophils, with a median of 12850/mm^3 (range 7880, 29140). Skin biopsy mainly showed subcorneal pustules (22 cases, 47.8%), spongy pustules (14 cases, 30.4%), and inflammatory cell infiltration (26 cases, 56.5%). Skin lesions disappeared in a median of 10 days (range 2, 42) after discontinuation of amoxicillin and administration of topical steroids (26 cases, 56.5%) as well as systemic corticosteroids (13 cases, 28.3%). *Conclusions*. AGEP is a rare complication of amoxicillin and is self-limiting. Clinicians should correctly identify AGEP and should avoid represcribing amoxicillin. Clinicians should correctly identify AGEP and avoid represcribing amoxicillin, which can prevent unnecessary treatment measures.

1. Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare and serious skin adverse reaction with a morbidity of only 1 to 5 in 1,000,000 [1]. AGEP is characterized by nonfollicular sterile pustules on an erythematous base and fever and can be induced by drugs, infection, foods, and xenobiotics [2]. More than 90% of patients with AGEP are related to drug intake [3, 4].

Penicillin is often associated with allergic reactions, with the most common adverse skin reactions being hives and rashes [5]. AGEP is a rare cutaneous adverse reaction to amoxicillin. What is known about amoxicillin-induced AGEP comes mainly from case reports. The clinical characteristics of amoxicillin-induced AGEP are unclear. The purpose of this study was to investigate the clinical characteristics of amoxicillin-induced AGEP and to provide evidence for the prevention and treatment of amoxicillin-induced AGEP by collecting related cases.

2. Methods

2.1. Retrieval Strategy. Case reports, case series, and clinical studies of amoxicillin-induced AGEP were collected by searching the Chinese and English databases from inception to January 31, 2023. These data include Wanfang, CNKI, China VIP, PubMed, Embase, and Cochrane Library. Search terms included amoxicillin, amoxicillin-clavulanic acid,

antibiotics, beta-lactam, acute localized exanthematous pustulosis, toxic pustoloderma, toxic pustulosis, pustulosis, exanthematous pustulosis, AGEP, ALEP, acute generalized exanthematous pustulosis, and drug reaction.

2.2. Inclusion and Exclusion Criteria. Case reports and case series were included, and reviews, mechanism studies, and duplicate reports were excluded.

2.3. Data Extraction. Basic information (gender, age, country, medical history, allergy history, skin history, concurrent medications, indication, route of administration, and drug class), clinical symptoms, laboratory tests (leukocyte count, neutrophil count, C-reactive protein, erythrocyte sink, culture, patch tests, skin prick tests, lymphocyte transformation tests, and IL-36RN gene), histopathology, treatment, and prognosis of patients were extracted according to self-designed tables.

2.4. Correlation Evaluation. European case-control surveillance of severe cutaneous adverse reactions (EuroSCAR) was used for correlation evaluation: score total <0: no AGEP, 1 ~ 4: possible, 5 ~ 7: probable, and 8 ~ 12: definite [1].

2.5. Statistical Analysis. SPSS-22.0 is used for statistical analysis of data. Continuous data are represented by median (minimum, maximum) values. Counting data are represented by n (%).

3. Results

3.1. Epidemiological Features. After screening according to inclusion and exclusion criteria, a total of 46 patients from 44 articles were included, including 23 (50.0%) male patients (Table 1). The patients had a median age of 40 years (range 1.4, 87) and were mainly from Europe (25 cases, 54.3%) and Asia (12 cases, 32.6%). Six patients (13.0%) had preexisting medical conditions, and 12 patients (26.1%) had other concomitant medications. Six patients (13.0%) had a history of preexisting skin conditions, including atopic dermatitis, acne, drug rash, pustular lesions, and psoriasis vulgaris. Six patients (13.0%) had a history of drug allergies, including amoxicillin and penicillin. Amoxicillin and amoxicillin/clavulanate were used in 23 patients (50.0%), respectively. The median duration of AGEP onset was 2.5 days (0.25, 28), including 30 (65.2%) patients within 3 days and 38 (82.6%) patients within 7 days.

3.2. Clinical Symptoms. The clinical symptoms of 46 patients were summarized in Table 2. Nonfollicular pustules were present in all patients, and erythema was present in 36 (78.3%) patients. Fever occurred in 32 (69.6%) patients with body temperature ranging from 37.4 to 40°C. Thirteen (28.3%) patients presented with pruritus, and eight (17.4%) patients presented with edema distributed in the legs, face, palms, and laryngeal regions. The burning sensation was observed in 4 (8.7%) patients, and purpura and conjunctival inflammation in 2 (4.3%) patients, respectively. The lesions were mainly distributed in extremities (21 cases, 45.7%) and trunk (20 cases, 43.5%), followed by face (15 cases, 32.6%), neck (15 cases, 32.6%), generalized (10 cases, 21.7%), and back and chest (10 cases, 21.7%). Oral mucosa was involved in 10 (21.7%) patients, and desquamation occurred in 17 (37.0%) patients. Ten (21.7%) patients involved other organs including liver (4 cases, 8.7%), renal (3 cases, 6.5%), hemodynamic instability (2 cases, 4.3%), and lung (1 case, 2.2%).

3.3. Laboratory Test. Leukocytosis was recorded in 31 patients with a median value of 15495/mm^3 (range 10800, 48700). Neutrophilia was observed in 22 (47.8%) patients with a median value of 12850/mm^3 (range 7880, 29140). C-reactive protein was described in 16 patients, and 15 (32.6%) of whom were elevated, with a median value of 138 mg/L (range 7.2, 323.4). Erythrocyte sedimentation rate was elevated in 4 (8.7%) of the 6 patients. Twenty (43.5%) patients underwent pustular culture, but only 1 (2.2%) patient developed bacterial infection.

Lymphocyte transformation tests (LTT) were positive in 2 (4.3%) patients, and patch tests were positive in 18 (39.1%) of 19 patients. Skin prick tests were positive in 2 (4.3%) patients. Mutations in the IL-36RN gene encoding the interleukin (IL)-36 receptor antagonist (IL-36Ra) were found in 4 (8.7%) patients.

3.4. Histopathology. The skin biopsies of 31 patients were summarized in Table 3. Histopathology revealed subcorneal pustule (22 cases, 47.8%), spongiform pustule (14 cases, 30.4%), acanthosis (4 cases, 8.7%), and necrotic keratinocytes (4 cases, 8.7%) in the epidermis. Dermis showed marked papillary edema (7 cases, 15.2%) and inflammatory cell infiltrate (26 cases, 56.5%). Inflammatory cell infiltration is characterized by mixed inflammatory infiltration consisting of lymphocyte infiltration, neutrophils, and eosinophils.

3.5. Treatment. The treatment and prognosis of 46 patients are summarized in Table 4. Amoxicillin was discontinued in 44 patients and was not described in 2 patients. Twenty-six (56.5%) patients received systemic corticosteroid therapy, and 13 (28.3%) patients received topical corticosteroid therapy. Antihistamines were used in 10 (21.7%) patients, and topical antibiotics were used in 4 (8.7%) patients. Three (6.5%) patients received retinoic acids, and one patient received etanercept and intravenous immunoglobulin, respectively. Forty-four (95.7%) patients recovered after comprehensive treatment in a median time of 10 days (range 2, 42), and 2 patients did not describe the outcome.

3.6. Correlation Evaluation. Thirty-seven (80.4%) patients were classified as AGEP, and 9 (19.6%) patients were classified as acute localized exanthematous pustulosis (ALEP). According to EuroSCAR's AGEP score system, 19 (41.3%) patients achieved 5–7 points, and 27 patients (58.7%) achieved 8–12 points.

Table 1: Basic characteristics of the 46 patients included.

Parameters	Results
Sex (45)[a]	
M	23 (50.0%)
F	22 (47.8%)
Age	
Years	40 (1.4, 87)[b]
Country	
China	11 (23.9%)
Germany	5 (10.9%)
Italy	3 (6.5%)
America	3 (6.5%)
Portugal	3 (6.5%)
UK	3 (6.5%)
Japan	3 (6.5%)
Australia	2 (4.3%)
Belgium	2 (4.3%)
Spain	2 (4.3%)
Netherlands	2 (4.3%)
Canada	1 (2.2%)
Denmark	1 (2.2%)
Greece	1 (2.2%)
Iran	1 (2.2%)
Poland	1 (2.2%)
Switzerland	1 (2.2%)
Turkey	1 (2.2%)
Types of drugs	
Amoxicillin	23 (50.0%)
Amoxicillin/clavulanate	23 (50.0%)
Route of administration (21)[a]	
Po	20 (43.5%)
Intravenous	1 (2.2%)
Onset time (43)[a]	
Days	2.5 (0.25, 28)[b]
Within 12 h	5 (10.9%)
1–3	25 (54.3%)
4–7	8 (17.4%)
8–28	5 (10.9%)
Medical history	
AF, CHD, COPD, CVA, DU, CHD, T2DM, kidney disease, hypertension, congenital cardiac valve defect, migraine with aura, and hypercholesterolemia	6 (13.0%)
Concurrent medications	12 (26.1%)
Medical histories of dermatologic	
Atopic dermatitis, acne, drug rash, pustular lesions, and psoriasis vulgaris	6 (13.0%)
Allergy history	
Amoxicillin and penicillin	6 (13.0%)
Indication (42)[a]	
Respiratory tract infection	17 (37.0%)
Surgical prophylaxis	5 (10.9%)
Dental prophylaxis	5 (10.9%)
Dental infection	5 (10.9%)
Urinary tract infection	2 (4.3%)
Skin soft tissue infection	2 (4.3%)
Arthritis	2 (4.3%)
Bartholin's cyst	1 (2.2%)
Otitis media	1 (2.2%)
Sinusitis	1 (2.2%)
Fever of unknown origin	1 (2.2%)

AF: atrial fibrillation; CHD: congestive heart failure; COPD: chronic obstructive pulmonary disease; CVA: cough variant asthma; CHD: coronary heart disease; DU: duodenal ulcers; T2DM: type 2 diabetes mellitus. [a]The number of patients out of 46 about whom information regarding this particular parameter was provided. [b]Median (minimum-maximum).

Table 2: Clinical characteristics of the 46 patients included.

Parameter	Result
Clinical symptoms	
Nonfollicular pustules	46 (100%)
Erythema	36 (78.3%)
Fever	32 (69.6%)
Pruritus	13 (28.3%)
Edema: eyelids legs, facial, palms, and laryngeal edema	8 (17.4%)
Burning pain	4 (8.7%)
Purpura	2 (4.3%)
Conjunctival inflammation	2 (4.3%)
Location of pustules	
Extremities	21 (45.7%)
Trunk	20 (43.5%)
Face	15 (32.6%)
Neck	15 (32.6%)
Generalized	10 (21.7%)
Back and chest	10 (21.7%)
Chin	4 (8.7%)
Groin	3 (6.5%)
Palms	3 (6.5%)
Genitalia	2 (4.3%)
Ankles	1 (2.2%)
Soles	1 (2.2%)
Nose	1 (2.2%)
Foot	1 (2.2%)
Temperature (37)[a]	
Normal	6 (13.0%)
Yes	31 (67.4%)
37.4–38°C	2 (4.3%)
38-39°C	9 (19.6%)
39-40°C	12 (26.1%)
Mucosal involvement	
Oral erosions	10 (21.7%)
Desquamation	17 (37.0%)
Systemic involvement (10)[a]	
Liver	4 (8.7%)
Renal	3 (6.5%)
Hemodynamic instability	2 (4.3%)
Lung	1 (2.2%)

[a]The number of patients out of 46 about whom information regarding this particular parameter was provided.

Table 3: Laboratory and histological examination of 46 patients included.

Parameter	Result
Laboratory test	
White blood cell (31)[a]	
Leukocytosis	31 (67.4%)
mm^3	15495 (10800, 48700)[b]
Neutrophil (22)[a]	
Neutrophilia	22 (47.8%)
mm^3	12850 (7880, 29140)[b]
C-reactive protein (16)[a]	
Normal	1 (2.2%)
Elevated	15 (32.6%)
mg/L	138 (7.2, 323.4)[b]
Erythrocyte sedimentation rate (6)[a]	
Normal	2 (4.3%)
Elevated	4 (8.7%)
Cultures (20)[a]	
Negative	19 (41.3%)
Positive	1 (2.2%)
Skin biopsy (31)[a]	
Epidermis	
Subcorneal pustule	22 (47.8%)
Spongy pustules	14 (30.4%)
Acanthosis	4 (8.7%)
Necrotic keratinocytes	4 (8.7%)
Derma	
Papillary edema	7 (15.2%)
Capillary thrombosis	1 (2.2%)
Inflammatory cell infiltrate	26 (56.5%)
Neutrophilic infiltrate	4 (8.7%)
Lymphohistiocytic infiltrate	2 (4.3%)
Eosinophils infiltrate	1 (2.2%)
Mixed inflammatory infiltrate	18 (39.1%)
Lymphocyte transformation tests (2)[a]	
Positive	2 (4.3%)
Patch tests (19)[a]	
Negative	1 (2.2%)
Positive	18 (39.1%)
Skin prick tests (3)[a]	
Positive	3 (6.5%)
IL-36RN gene (4)[a]	
p.Leu27Pro	1 (2.2%)
p.Ser113Leu	1 (2.2%)
c.C338T:p.S113L	1 (2.2%)
p.Arg10X and p.Arg10ArgfsX1	1 (2.2%)

[a]The number of patients out of 46 about whom information regarding this particular parameter was provided. [b]Median (minimum-maximum).

4. Discussion

Several drugs have been reported in association with AGEP, such as pristinamycin, quinolones, hydroxychloroquine, sulfonamides, terbinafine, diltiazem, ketoconazole, and fluconazole [6]. The clinical characteristics of AGEP induced by different drugs may be different. AGEP can occur at any age and seems to be more common in women [1]. Amoxicillin-induced AGEP appeared in both male and female patients with no gender difference. The mean duration of drug-induced AGEP depends on the drug class. AGEP can be triggered 1 day after a burst of antibiotics and an average of 11 days after exposure to other nonantibiotic drugs. 6 Diltiazem-induced AGEP ranged from 1 day to 3 weeks, whereas terbinafine-induced AGEP ranged from 1 day to 77 days [7, 8]. Amoxicillin-induced AGEP ranged from 6 h to 28 d after administration. This may suggest that the pathogenesis of AGEP is different for different drug-induced AGEP.

The severity, laboratory tests, and prognosis of AGEP caused by different drugs may vary. Laboratories for AGEP caused by other drugs found hypocalcemia in some cases and eosinophilia in 30% of cases [9]. In rare cases, AGEP may also be associated with life-threatening systemic

Table 4: Treatment and prognosis of the 46 patients included.

Parameter	Result
Treatment	
Discounted	44 (95.7%)
Unspecified	2 (4.3%)
Systemic corticoid	26 (56.5%)
Topical corticosteroids	13 (28.3%)
Antihistamines	10 (21.7%)
Topical antibiotic therapy	4 (8.7%)
Etanercept	1 (2.2%)
Retinoic acids	3 (6.5%)
Intravenous immunoglobulin	1 (2.2%)
Outcome	
Resolved	44 (95.7%)
Unspecified	2 (4.3%)
Recovery time (37)[a]	
Days	10 (2, 42)[b]
AGEP type	
AGEP	37 (80.4%)
ALEP	9 (19.6%)
EuroSCAR AGEP score*	
5–7	19 (41.3%)
8–12	27 (58.7%)

AGEP: acute generalized exanthematous pustulosis; ALEP: acute localized exanthematous pustulosis; EuroSCAR: European case-control surveillance of severe cutaneous adverse reactions. [a]The number of patients out of 46 about whom information regarding this particular parameter was provided. [b]Median (minimum-maximum). *1–4: possible; 5–7: probable; 8–12 points: definite.

symptoms, including cholestasis, nephritis, and lung and bone marrow involvement, with mortality rates as high as 5% [2]. ALEP is a rare variant of AGEP in which lesions are usually confined to the face, neck, or chest [10, 11]. Amoxicillin-clavulanic acid and amoxicillin are the most commonly reported causes of ALEP cases compared to other drugs [12]. About 20% of patients have amoxicillin-induced ALEP. Most current studies on different drug-induced AGEP have been limited to observational or case reports with small sample sizes. Future multicenter, large-sample studies are needed to clarify the clinical characteristics of AGEP induced by different drugs.

The possibility of other drugs inducing AGEP cannot be ruled out, as 26% of patients were taking multiple drugs simultaneously. Clavulanic acid can also induce acute systemic erythematous impetigo [13]. Other drugs have been reported to be associated with AGEP, such as acetylsalicylic acid, ibuprofen, gliclazide, acarbose, and prednisolone [14–18]. The determination of amoxicillin as the primary cause of AGEP is based on the timing of the onset of AGEP and the sequence of medications taken, as well as the improvement of symptoms after withdrawal.

The diagnosis of AGEP is confirmed by clinical presentation, histopathological examination, and patch test [1]. Amoxicillin-induced AGEP is characterized by an acute and extensive pustular exanthema composed of numerous small, mostly nonfollicular, sterile pustules on erythematous skin, while erythroderma is common but not widespread in AGEP. The rash is distributed on the extremities, trunk, and face. AGEP patients are often accompanied by fever, with body temperature generally above 38°C, and only a few patients have mucosal damage. Patients with amoxicillin-induced AGEP fever had a temperature of up to 40°C. Mucous membranes were involved in about 22% of patients. Systemic involvement occurs in about 20% of patients, mostly involving liver, kidney, and lung function. Severe AGEP patients may experience multiple organ dysfunction and even death [19]. Liver, kidney, and lung involvement occurred in 22% of amoxicillin-induced AGEP patients. Leukocytosis and elevated neutrophil count (>7500/mm^3) are another important characteristic of AGEP [1]. The neutrophil count exceeded 7500/mm^3 in all patients with amoxicillin-induced AGEP.

Little is known about cross-reactivity in beta-lactam-induced AGEP. For pinpointing the culprit drug, cutaneous patch testing can prove helpful in contrast to other adverse drug eruptions and should be performed earliest 6 weeks after complete resolution. The sensitivity of patch testing is reported to be around 50–58% [20]. In addition, LTT, intradermal tests, and skin prick tests are also helpful in finding sensitizing drugs [21]. The LTT may be more sensitive than the patch test, especially in cases caused by beta-lactam antibiotics, and can help identify the culprit drug [22]. Patch tests help to identify multiple positive reactions to penicillin, aminopenicillin, and cephalosporin and provide specific avoidance indications. Mysore et al. reported one case of AGEP relapsing in a patient using piperacillin, ceftazidime, and meropenem [23]. Some patients showed only positive for penicillin antibiotics and negative for cephalosporins. 20 Although the patch test was negative for cephalosporins, we advise patients to use them with caution.

AGEP may be confused with other diseases, leading to misdiagnoses, such as generalized pustular psoriasis (GPP), Stevens–Johnson syndrome, toxic epidermal necrolysis, subcorneal pustular dermatosis, bullous impetigo, and hypersensitivity syndrome reaction [19]. AGEP is clinically similar to GPP of the von Zumbusch type, and it is difficult to distinguish between the two. However, a history of psoriasis, prolonged fever, differentiated histopathological picture, and no history of drug exposure contributed to the diagnosis of GPP [6].

The exact pathogenesis of AGEP remains a mystery. AGEP is a T-lymphocyte-mediated delayed-type hypersensitivity response confirmed by patch tests and in vitro tests [24]. Pathogenic agents (mainly drugs) come into contact with the body and activate specific CD4+ and CD8 + T lymphocytes via antigen-presenting cells. The activated lymphocytes enter the dermis and epidermis and release large amounts of the neutrophil chemotactic factor interleukin 8 (IL-8) to further neutrophil chemotactic into the blister and eventually form sterile pustules [25]. IL-36RN mutations have been associated with a variety of aseptic impetigo, such as GPP and impetigo herpetiformis [26, 27]. In recent years, IL-36RN gene mutation has been found to be associated with some AGEP patients. IL-36RN is responsible for encoding the IL-36 receptor antagonist (IL-36Ra). IL-36RN is responsible for encoding the high expression of the IL-36 receptor antagonist (IL-36Ra) in

the epithelial tissues of the skin. Structural changes in IL-36Ra lead to uncontrolled IL-36 signaling when IL-36RN is mutated, activating downstream proinflammatory signaling pathways that lead to impetigo eruptions [1, 28]. Patients with IL-36RN variants were more likely to have mucosal involvement [29, 30]. Conversely, oral mucosal involvement may be a clinical clue to potential mutations in IL-36RN. More studies are needed to confirm whether IL-36RN mutation is the molecular genetic basis of AGEP.

The optimal treatment plan for AGEP is still not determined, and discontinuation of suspect drugs is the most important means. Topical disinfection and wetting dressings as well as topical corticosteroids may be an effective means, and topical corticosteroids may also be effective for severe itching [19]. Systemic glucocorticoids need to be used in severe cases, and skin lesions usually subside within a few days. There is a lack of high-quality evidence on the dose and duration of systemic glucocorticoid therapy. Different drug-induced AGEP resolution times differ, which may be related to the half-life of the drug. For example, the 40–50 days half-life of hydroxychloroquine results in AGEP resolution times ranging from 7 to 81 days [31]. Amoxicillin-induced AGEP symptoms usually resolve spontaneously within 2–42 days. Although there is a lack of clinical evidence for the use of immunosuppressants, cyclosporine and etanercept are often administered in common practice with significant clinical results [32, 33]. IL-36 receptor antagonists may play an important role in the treatment of AGEP. Spesolimab is an IL-36 receptor antagonist approved for the treatment of GPP flares in adults [34]. AGEP is self-limited and has a good prognosis. However, reexposure to the same trigger may also lead to another episode of AGEP [35–37].

5. Conclusion

AGEP is a very rare complication of amoxicillin and differs from other acute episodes of GPP. Clinicians should promptly discontinue and avoid readministering amoxicillin once patients develop AGEP. AGEP is self-limiting, and topical corticosteroids reduce the duration of hospitalization. The evidence for systemic corticosteroid therapy in the treatment of AGEP is unclear.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study did not require ethical board approval because the study was a retrospective study and did not involve sensitive personal information.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by the Scientific Research Fund Project of Hunan University of Chinese Medicine (grant number 2022XYLH004).

References

[1] A. Sidoroff, S. Halevy, J. N. Bavinck, L. Vaillant, and J. C. Roujeau, "Acute generalized exanthematous pustulosis (AGEP)--a clinical reaction pattern," *Journal of Cutaneous Pathology*, vol. 28, no. 3, pp. 113–119, 2001.

[2] L. Feldmeyer, K. Heidemeyer, and N. Yawalkar, "Acute generalized exanthematous pustulosis: pathogenesis, genetic background, clinical variants and therapy," *International Journal of Molecular Sciences*, vol. 17, no. 8, p. 1214, 2016.

[3] J. C. Roujeau, P. Bioulac-Sage, C. Bourseau, J. C. Guillaume, P. Bernard, and C. Lok, "Acute generalized exanthematous pustulosis. Analysis of 63 cases," *Archives of Dermatology*, vol. 127, no. 9, pp. 1333–1338, 1991.

[4] S. L. Chang, Y. H. Huang, C. H. Yang, S. Hu, and H. S. Hong, "Clinical manifestations and characteristics of patients with acute generalized exanthematous pustulosis in Asia," *Acta Dermatologica Venereologica*, vol. 88, no. 4, pp. 363–365, 2008.

[5] E. S. Shenoy, E. Macy, T. Rowe, and K. G. Blumenthal, "Evaluation and management of penicillin allergy: a review," *Journal of the American Medical Association*, vol. 321, no. 2, pp. 188–199, 2019.

[6] A. Sidoroff, A. Dunant, C. Viboud et al., "Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR)," *British Journal of Dermatology*, vol. 157, no. 5, pp. 989–996, 2007.

[7] M. Fernández-Ruiz, F. López-Medrano, F. García-Ruiz, and J. L. Rodríguez-Peralto, "Diltiazem-induced acute generalized exanthematous pustulosis: a case report and review of the literature," *Actas Dermatology-Sifiliográficas*, vol. 100, no. 8, pp. 725–727, 2009.

[8] T. Wu, Y. He, Z. Fan, W. Sun, Z. Li, and C. Wang, "Clinical manifestations and management of terbinafine-induced acute generalized exanthematous pustulosis," *Dermatologic Therapy*, vol. 2023, Article ID 3650952, 8 pages, 2023.

[9] C. Hotz, L. Valeyrie-Allanore, C. Haddad et al., "Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients," *British Journal of Dermatology*, vol. 169, no. 6, pp. 1223–1232, 2013.

[10] H. S. Sim, J. E. Seol, J. S. Chun, J. K. Seo, D. Lee, and H. S. Sung, "Acute localized exanthematous pustulosis on the face," *Annals of Dermatology*, vol. 23, no. Suppl 3, pp. S368–S370, 2011.

[11] M. Mohamed, Y. Soua, L. Njim et al., "Acute localized exanthematous pustulosis on the face: 6 cases in Tunisia," *Annals of Dermatology and Venereology*, vol. 141, no. 12, pp. 756–764, 2014.

[12] I. Safa, L. Ines, L. Noureddine et al., "Acute localized exanthematous pustulosis: clinical features, pathophysiology, and therapy," *Dermatologic Therapy*, vol. 34, no. 5, 2021.

[13] L. Amaral, L. Carneiro-Leão, and J. R. Cernadas, "Acute generalized exanthematous pustulosis due to clavulanic acid," *Journal of Allergy and Clinical Immunology: In Practice*, vol. 8, no. 3, pp. 1083-1084, 2020.

[14] A. Bahuguna, "Acute generalized exanthematous pustulosis: a rare side effect of a common over-the-counter drug,

Acetylsalicylic acid," *Indian Dermatology Online Journal*, vol. 4, no. 3, pp. 231–233, 2013.

[15] D. Belz, O. D. Persa, S. Haese, and N. Hunzelmann, "Acute generalized exanthematous pustulosis caused by ibuprofen-Diagnosis confirmed by patch testing," *Contact Dermatitis*, vol. 79, no. 1, pp. 40-41, 2018.

[16] M. Contreras-Steyls, F. Vílchez-Márquez, A. Mota, B. Moyano, and E. Herrera-Ceballos, "Acute generalized exanthematous pustulosis induced by gliclazide: a case report," *International Journal of Dermatology*, vol. 52, no. 12, pp. 1591–1593, 2013.

[17] S. Arianayagam, E. Ieremia, and S. Arnold, "Acute generalised exanthematous pustulosis secondary to prednisolone: an unlikely suspect," *European Journal of Dermatology*, vol. 31, no. 1, pp. 119–121, 2021.

[18] C. S. Wu, W. Y. Chang, C. C. Lan, G. S. Chen, and H. H. Chiu, "Acute generalized exanthematous pustulosis possibly induced by acarbose," *International Journal of Dermatology*, vol. 47, no. 12, pp. 1313–1315, 2008.

[19] J. Szatkowski and R. A. Schwartz, "Acute generalized exanthematous pustulosis (AGEP): a review and update," *Journal of the American Academy of Dermatology*, vol. 73, no. 5, pp. 843–848, 2015.

[20] P. C. Stadler, A. Oschmann, K. Kerl-French et al., "Acute generalized exanthematous pustulosis: clinical characteristics, pathogenesis, and management," *Dermatology*, vol. 239, no. 3, pp. 328–333, 2023.

[21] C. Mayorga, G. Celik, P. Rouzaire et al., "In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI drug allergy interest group position paper," *Allergy*, vol. 71, no. 8, pp. 1103–1134, 2016.

[22] M. M. Speeckaert, R. Speeckaert, J. Lambert, and L. Brochez, "Acute generalized exanthematous pustulosis: an overview of the clinical, immunological and diagnostic concepts," *European Journal of Dermatology*, vol. 20, no. 4, pp. 425–433, 2010.

[23] V. Mysore and A. Ghuloom, "A case of recurrent acute generalized exanthematous pustulosis due to beta-lactam antibiotics: a case report," *Journal of Dermatological Treatment*, vol. 14, no. 1, pp. 54–56, 2003.

[24] A. Moreau, A. Dompmartin, B. Castel, B. Remond, and D. Leroy, "Drug-induced acute generalized exanthematous pustulosis with positive patch tests," *International Journal of Dermatology*, vol. 34, no. 4, pp. 263–266, 1995.

[25] M. Britschgi, U. C. Steiner, S. Schmid et al., "T-cell involvement in drug-induced acute generalized exanthematous pustulosis," *Journal of Clinical Investigation*, vol. 107, no. 11, pp. 1433–1441, 2001.

[26] K. Sugiura, "The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants," *Journal of Dermatological Science*, vol. 74, no. 3, pp. 187–192, 2014.

[27] K. Sugiura, N. Oiso, S. Iinuma et al., "IL36RN mutations underlie impetigo herpetiformis," *Journal of Investigative Dermatology*, vol. 134, no. 9, pp. 2472–2474, 2014.

[28] S. Kumar, P. C. McDonnell, R. Lehr et al., "Identification and initial characterization of four novel members of the interleukin-1 family," *Journal of Biological Chemistry*, vol. 275, no. 14, pp. 10308–10314, 2000.

[29] A. A. Navarini, L. Valeyrie-Allanore, N. Setta-Kaffetzi et al., "Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis," *Journal of Investigative Dermatology*, vol. 133, no. 7, pp. 1904–1907, 2013.

[30] S. Marrakchi, P. Guigue, B. R. Renshaw et al., "Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis," *New England Journal of Medicine*, vol. 365, no. 7, pp. 620–628, 2011.

[31] K. C. Pearson, D. S. Morrell, S. R. Runge, and P. Jolly, "Prolonged pustular eruption from hydroxychloroquine: an unusual case of acute generalized exanthematous pustulosis," *Cutis*, vol. 97, no. 3, pp. 212–216, 2016.

[32] V. Di Lernia, L. Grenzi, E. Guareschi, and C. Ricci, "Rapid clearing of acute generalized exanthematous pustulosis after administration of ciclosporin," *Clinical and Experimental Dermatology*, vol. 34, no. 8, pp. e757–e759, 2009.

[33] A. Sadighha, "Etanercept in the treatment of a patient with acute generalized exanthematous pustulosis/toxic epidermal necrolysis: definition of a new model based on translational research," *International Journal of Dermatology*, vol. 48, no. 8, pp. 913-914, 2009.

[34] H. A. Blair, "Spesolimab: first approval," *Drugs*, vol. 82, no. 17, pp. 1681–1686, 2022.

[35] D. Shuttleworth, "A localized, recurrent pustular eruption following amoxycillin administration," *Clinical and Experimental Dermatology*, vol. 14, no. 5, pp. 367-368, 1989.

[36] E. Syrigou, D. Grapsa, A. Charpidou, and K. Syrigos, "Acute generalized exanthematous pustulosis induced by amoxicillin/clavulanic acid: report of a case presenting with generalized lymphadenopathy," *Journal of Cutaneous Medicine and Surgery*, vol. 19, no. 6, pp. 592–594, 2015.

[37] A. Ozkaya-Parlakay, D. Azkur, A. Kara et al., "Localized acute generalized exanthematous pustulosis with amoxicillin and clavulanic acid," *Turkish Journal of Pediatrics*, vol. 53, no. 2, pp. 229–232, 2011.