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CASE SERIES

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Acute Generalized Exanthematous Pustulosis (AGEP) Unveiled: A Tertiary Hospital Case Series on Antibiotic-Induced Adverse Drug Reactions in Davao City, Philippines

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a rare and severe cutaneous adverse reaction (SCAR) characterized by the rapid onset of widespread small sterile pustules on erythematous skin. It is only estimated to occur in 1 to 5 cases per million annually worldwide. It is distinguishable from other SCARs based on the time interval between drug intake and the onset of symptoms. This characteristic time interval is a key factor in differentiating AGEP from other skin reactions.

This case series presents three distinct cases of AGEP in patients admitted to a tertiary hospital in Davao City, Philippines. Our cases demonstrate the diverse clinical presentations and triggers of AGEP, primarily involving antibiotics, including ceftriaxone, piperacillin-tazobactam, clindamycin, and amoxicillin. The three cases share similarities in demographic profiles, with patients being female in the 26 to 60 age group; however, they exhibit variations in the onset of symptoms relative to drug exposure, notably appearing 1 day, 4 days, and 24 days following antibiotic use. All patients had no mucosal and organ involvement. Treatment strategies of our patients involved identification and discontinuation of the offending medication, application of topical steroids, and providing supportive care. All three patients had resolution of the skin lesions.

Because AGEP exhibits a distinctive and rapidly evolving clinical presentation, it is primarily diagnosed based on clinical findings. All three patients presented rapid eruption of multiple, small, non-follicular pustules on a background of an erythematous exanthem following drug exposure. The most commonly implicated agents causing AGEP include antibiotics. Beta-lactams are the main offenders in this case series. This case series underscores the importance of recognizing AGEP as a potential adverse reaction to antibiotics and the need for prompt identification, withdrawal of the offending medication, and timely initiation of treatment to ensure favorable outcomes. This article highlights the importance of diagnosis and management of AGEP as well as clinical vigilance in underreported regions like the Philippines, where there is limited data.

Keywords: Acute generalized exanthematous pustulosis (AGEP), Non-follicular pustules, ceftriaxone, clindamycin, piperacillin-tazobactam, severe adverse drug reaction

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rare and severe cutaneous adverse reaction (SCAR) clinically characterized by rapid development and widespread occurrence of small, mostly non-follicular, sterile pustules on erythematous skin. Worldwide, the occurrence rate of AGEP falls within the range of 1 to 5 cases per million annually.[1] The incidence of AGEP in the United States is five cases per million people.[2] In Asia, specifically in Malaysia, AGEP is ranked as the third most common type of SCAR phenotype encountered. In Singapore, it is ranked second.[3]

Unfortunately, there is little published data regarding AGEP in the Philippines. Guzman and Paliza conducted a single retrospective study in 2018 involving SCAR patients from 2011 to 2015. In this study, 14 per 10,000 patients had AGEP with a prevalence rate of only 1.25%.[4] To our knowledge, no published data regarding AGEP in the Mindanao region exists. This might be due to the disease being underreported and underrecognized.

This case series will describe the demographic profiles, clinical presentation, different antibiotic exposure histories, and treatment outcomes of patients with AGEP in a tertiary hospital in Davao City to help clinicians diagnose AGEP based on clinical findings for prompt identification, immediate withdrawal of the offending medication, and timely initiation of appropriate management.

CASE SERIES

Case 1

A 33-year-old Filipino female from Calinan, Davao City, was brought to the ER for right lower quadrant pain. Three days before admission, the patient had a sudden onset of vague, non-radiating right lower quadrant pain (scale 3/10) associated with anorexia, vomiting, and undocumented febrile episodes. She initially tolerated her condition. Gradual worsening of abdominal pain, increasing to a pain scale of 7/10, prompted consultation, and she was subsequently admitted as a case of acute appendicitis under General Surgery. She was a known diabetic with poor compliance with insulin therapy. She denied smoking, drinking alcoholic beverages, and illicit drug use. The patient had no known food and drug allergies and is unvaccinated against COVID-19 infection.

She was initially managed as a case of acute appendicitis and was started on ceftriaxone 2 grams once daily via intravenous route. On day 4 of the antibiotic, there was a new onset of multiple non-follicular pustules on her back, and she complained of pruritus. Twenty-four hours later, these lesions became generalized, now involving her face, trunk, back, and lower & upper extremities. The main service considered a hypersensitivity reaction; hence, the patient was referred to Allergology and Immunology for co-management and Dermatology for a skin punch biopsy.

On assessment by the Allergology service, she was seen awake, not in cardiorespiratory distress, with the following vital signs: 100/70 mmHg, tachycardic at 108 beats/minute, slightly tachypneic at 21 cycles/minute with an O2 saturation of 98% at room air, and afebrile at 36.8°C. She has a body mass index of 21.87 kg/m² (normal by Asia Pacific classification). Upon admission, she had an elevated white blood cell (WBC) count (13,480/μL) due to appendicitis. She had an increase in WBC count of 15,190/μL (with 8,200/μL of polymorphonuclear neutrophils) during the onset of skin lesions. She also had mild anemia with a hemoglobin level of 10.4.0 g/dL. She was thrombocytopenic with a platelet count of 109,000/μL, aspartate aminotransferase of 17.71 IU/L, alanine aminotransferase of 11.65 IU/L, five times elevated total bilirubin of 6 mg/dL, elevated alkaline phosphatase of 264.35 IU/L, elevated blood urea nitrogen of 85.97 mg/dL, and elevated serum creatinine of 5.67 mg/dL.

Physical examination revealed numerous small, non-follicular pustules on erythematous skin in the face, trunk, back, and lower and upper extremities (Figure 1). No mucosal involvement was noted. The patient was managed as a case of acute generalized exanthematous pustulosis caused by ceftriaxone.

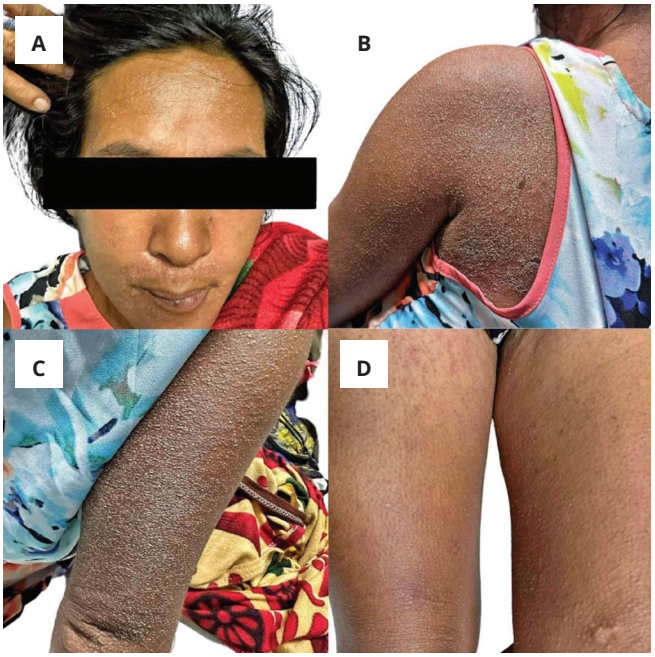

Figure 1. Multiple, small, non-follicular, pustules on erythematous skin in the face **(A)**, back **(B)**, upper **(C)** and lower extremities **(D)** post-exposure to Ceftriaxone.

A skin biopsy with hematoxylin-eosin stain was done, showing sections of basketweave stratum corneum with subcorneal collections of neutrophils, lymphocytes, and histiocytes overlying a spongiotic epidermis with psoriasiform hyperplasia (Figure 2). The superficial dermis revealed edema and moderate to dense interstitial and perivascular inflammatory infiltrates composed predominantly of lymphocytes, histiocytes, and eosinophils. Dilated blood vessels with intraluminal eosinophils and melanophages were likewise seen. The histopathologic diagnosis was spongiotic psoriasiform dermatitis with subcorneal pustules with eosinophilic infiltrates in the dermis, suggestive of acute generalized exanthematous pustulosis.

The eruption of lesions occurred on day 4 of ceftriaxone. The offending drug was discontinued on day 7 upon assessment of the Allergology and Dermatology services, and she was started on bilastine 20 mg/day and topical application of petroleum jelly 25 g + 5 g tube of clobetasol twice daily for 7 days. The antibiotic was shifted to piperacillin-tazobactam 4.5 grams intravenous infusion every 8 hrs. Twenty-four hours after discontinuation of ceftriaxone, there was drying of the lesions with a decrease in the pruritus. Seventy-two hours after discontinuing ceftriaxone, there was a beginning desquamation of the facial and trunk lesions. No new eruptions were noted from hospital day 8 to 13. Additionally, five days after the discontinuation of ceftriaxone, there was a generalized resolution of lesions, as seen in Figure 3. Desquamation and minimal scaling were noted post-treatment of the generalized pustules.

Case 2

A 60-year-old Filipino female from Catalunan Grande, Davao City, was seen in the ER for swelling of the posterior neck. Three weeks before admission, the patient had a solitary purulent lesion at the posterior neck area with a palpable 2 x 3 cm fluctuant mass associated with undocumented fever and generalized weakness. She initially tolerated the condition, but persistence prompted consultation in our institution. She has diabetes mellitus type 2 - insulin requiring but with poor compliance. She was a non-smoker, non-alcoholic beverage drinker, and had no illicit drug use. She did not receive COVID-19 vaccination and denied any food or drug allergies.

On admission, the patient was awake, not in respiratory distress, with the following vital signs: 100/60 mmHg, heart rate of 80 beats/minute, slightly tachypneic at 21 cycles/minute with oxygen saturation of 98% at room air, and febrile at 39.1°C. Her body mass index was 25.63 kg/m^2 (Obese I by Asia Pacific Classification). Pertinent physical examination findings included an erythematous, fluctuant, and tender mass on her posterior neck. Other examinations were generally unremarkable.

The patient was managed as a case of sepsis secondary to posterior neck abscess and uncontrolled diabetes mellitus type 2 – insulin-requiring. She was immediately started on clindamycin 600 mg through intravenous infusion every 6 hours and piperacillin-tazobactam 4.5 grams through intravenous infusion every 6 hours. Other medications started in this patient include omeprazole 40 mg intravenous infusion once daily, tramadol 50 mg intravenous infusion, and insulin 70/30 28 units subcutaneously in the morning, 28 units subcutaneously at night.

On antibiotic day 24, there was an appearance of areas of red skin studded with pinhead-sized sterile pustules over the abdomen and chest (Figure 4). These symptoms were associated with pain (scale of 5/10), pruritus, and a fever of 38.6°C. No associated mucosal involvement was noted. She had an elevated WBC count of 10,030/µL (with 7,300/µL of polymorphonuclear neutrophils) during the onset of skin lesions from a baseline of 12,090/µL. She also had moderate anemia with a hemoglobin level of 9.4 g/dL, platelet count of 327,000/µL, aspartate aminotransferase of 31.6 IU/L, alanine aminotransferase of 15.91 IU/L, blood urea nitrogen of 13.61 mg/dL, serum creatinine of 0.5 mg/dL, and a new onset elevated C-reactive protein (CRP) level of 2.41 mg/dL.

The patient was then referred to the Allergology and Immunology and Dermatology services. She was managed as a case of acute generalized exanthematous pustulosis secondary to piperacillin-tazobactam vs clindamycin. These suspected drugs were immediately discontinued, and the patient was started on bilastine 40 mg/day and hydrocortisone 1% lotion applied on affected areas twice daily for 7 days. The patient was instructed to halt the use of liniment oils, start using unscented soap, and practice proper hygiene daily.

Three days after discontinuing piperacillin-tazobactam and clindamycin, multiple erythematous macules, pustules, and papules were still present on the chest and abdomen (Figure 5). Hydrocortisone lotion was discontinued and shifted to betamethasone valerate lotion. The patient was instructed to use unscented and gentle lotion and apply it twice or thrice daily. Four days off antibiotics, there was a decrease in the erythematous base and the beginning resolution of the papules and macules. Five days after discontinuation of antibiotics, pruritus was resolved with no new onset lesions. Resolution of symptoms occurred seven days after discontinuation of antibiotic. Thus, she was advised to discontinue betamethasone valerate lotion and to continue unscented gentle lotion application thrice daily.

Case 3

A case of a 26-year-old Filipino female from Buhangin, Davao City, who came in due to generalized rashes. Twelve

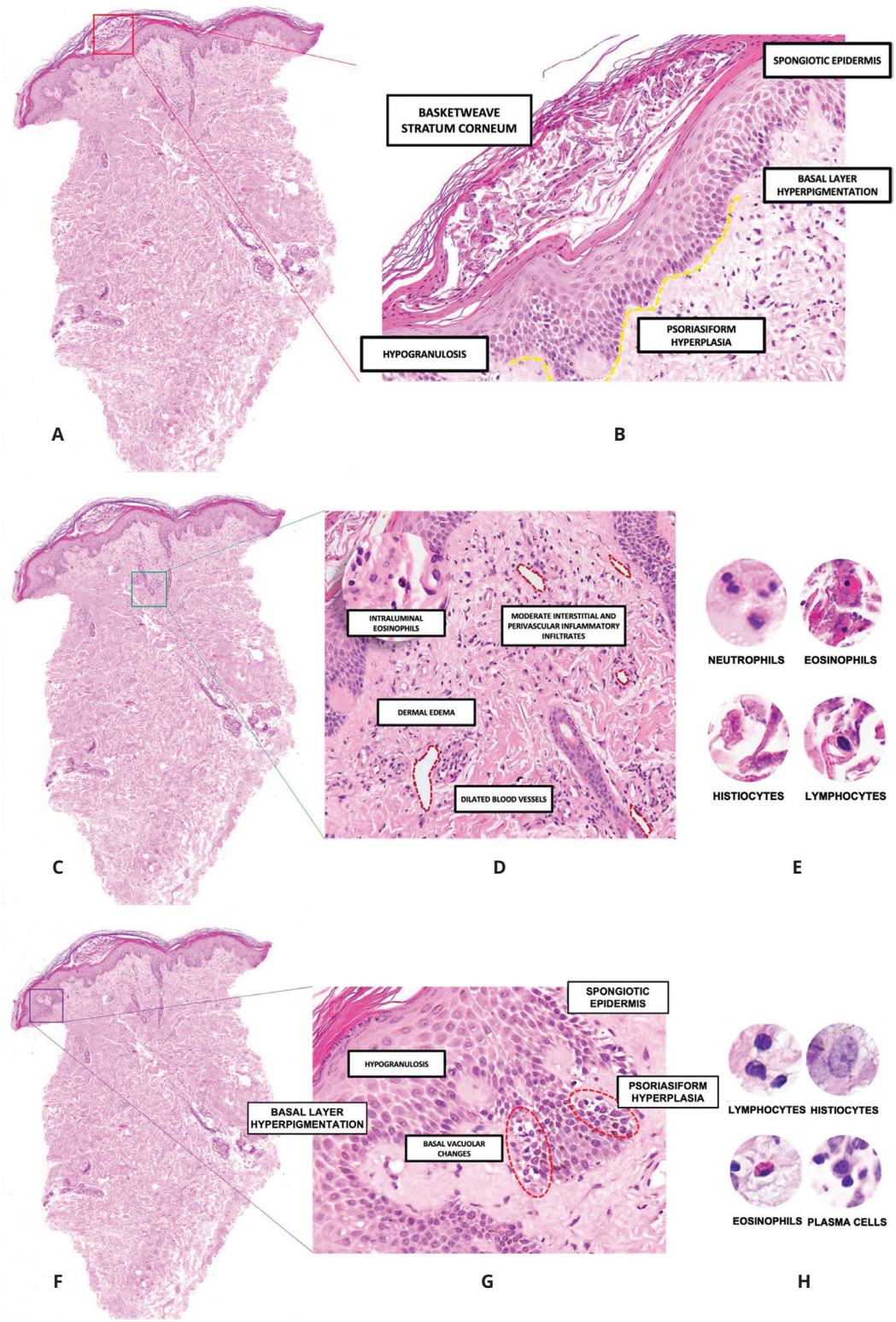

Figure 2. Photomicrograph of Case 1 skin biopsy showing sections of basketweave stratum corneum [H&E, 400x **(A)** and 1000x **(B)**] and spongiotic epidermis with psoriasiform hyperplasia [H&E, 400x **(A)** and 1000x **(B)**]; skin biopsy showing a section where superficial dermis is edematous and moderate to dense interstitial and perivascular inflammatory infiltrates [H&E, 400x **(C)**, 1000x **(D)**] composed predominantly of lymphocytes, histiocytes, and eosinophils **(E)**. Dilated blood vessels with intraluminal eosinophils and melanophages are likewise seen; skin biopsy showing a section of subcorneal collections of neutrophils, lymphocytes, and histiocytes overlying a spongiotic epidermis with psoriasiform hyperplasia [H&E, 400x **(F)** and 1000x **(G) (H)**].

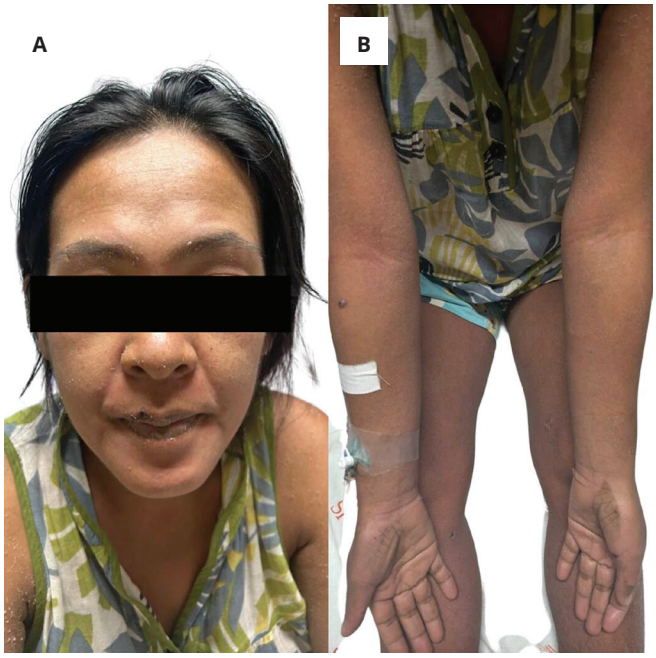

Figure 3. Resolution of generalized exanthematous pustules with minimal skin desquamation on face **(A)** and extremities **(B)**.

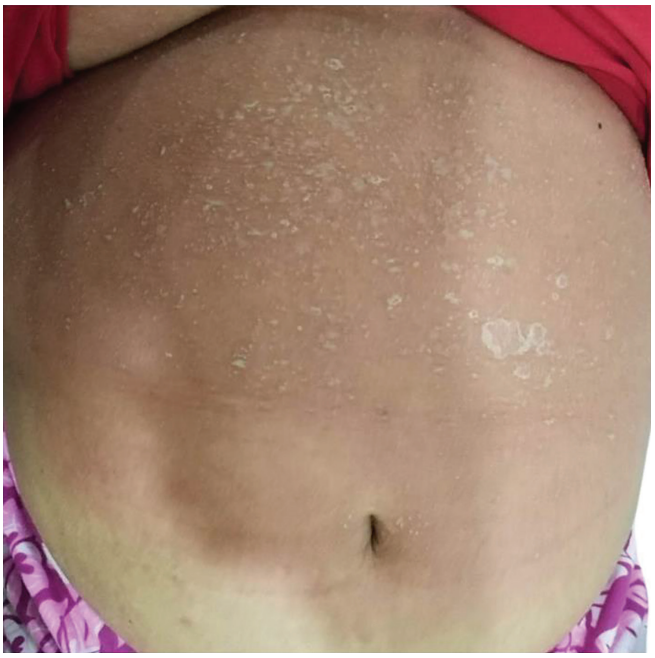

Figure 4. Case number 2 showing the appearance of areas of red skin studded with pinhead-sized sterile pustules in the chest and abdomen (onset of lesions).

days before admission, the patient was discharged from our institution after giving birth to her first child. She was given amoxicillin 2 grams/day and mefenamic acid 1500 mg/day as take-home medications, which the patient took with good compliance. The patient started to notice pruritic erythematous flat lesions on the lower extremities on day 1 of antibiotic use. The patient opted to continue her medications and did not seek any consultation. On day 5 of antibiotic use, the patient noticed the persistence of symptoms now associated with facial and bilateral extremity edema. She then stopped taking the amoxicillin and mefenamic acid medications and self-medicated with loratadine which afforded temporary relief of symptoms. Three days before admission, the patient still noted the presence of pruritic erythematous flat lesions, which now involved her upper and lower extremities. She mentioned that she started to use sulfur soap. The patient then noticed the evolution of symptoms, with a generalized pustular and erythematous base, as claimed. This prompted consultation at our institution. She has diabetes mellitus type 2 - non-insulin requiring. She has no known food or drug allergies. She was a previous smoker and an occasional alcoholic beverage drinker but denies illicit drug use. The patient also had not received any COVID-19 vaccines.

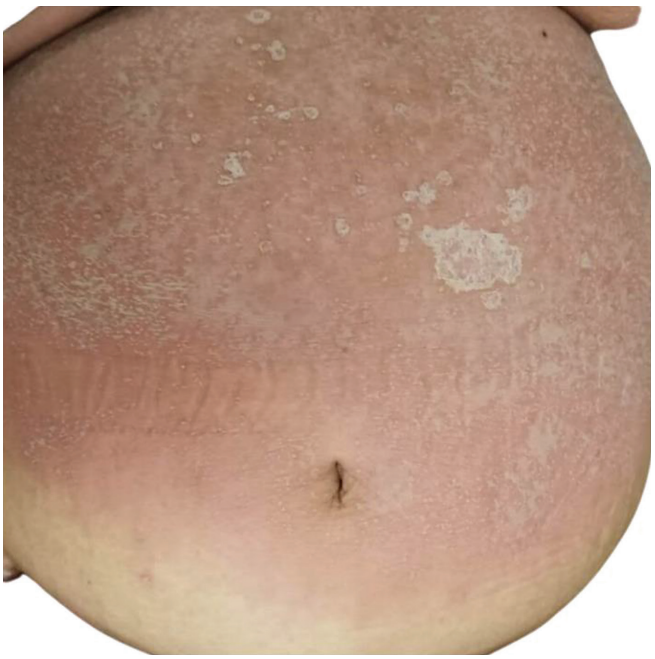

Figure 5. Case number 2 on Day 3 post-exposure to antibiotics.

The patient came into the emergency department with a normal blood pressure of 112/72 mmHg, tachycardic at 132 beats/minute, normal respiratory rate, afebrile at 36.9°C, and an oxygen saturation of 98% at room air. She weighed 65 kg, had a height of 157 cm, and had a body mass index of 26.4 kg/m^2 (Obese I by Asia Pacific Classification). The patient was examined awake and not in respiratory distress. Physical examination was generally unremarkable except when assessing the skin, where there was desquamation in the neck, trunk, and back. There was also a note of erythematous patches in the lower and upper

extremities. No mucosal lesions were noted. On admission, she had an elevated WBC count of 10,820/μL (with 7,400/μL of polymorphonuclear neutrophils), a hemoglobin level of 14.1 g/dL, platelet count of 319,000/μL, aspartate aminotransferase of 20.2 IU/L, alanine aminotransferase of 38.5 IU/L, blood urea nitrogen of 4.0 mg/dL, serum creatinine of 0.86 mg/dL, and an elevated CRP level of 5.61 mg/dL.

The patient was taking amoxicillin before the onset of pruritic lesions and only stopped taking the medications after seven days. Given the history of multiple disseminated pustules on an erythematous background, she was managed as a case of acute generalized exanthematous pustulosis secondary to amoxicillin use. The patient was then started immediately on levocetirizine 5 mg/day, hydrocortisone 100 mg intravenously every 6 hours for 8 doses, and betamethasone lotion applied every 12 hours. During the admission, there was no note of new-onset lesions. Desquamation of the skin in the face, trunk, back, lower, and upper extremities on hospital day 2 and subsequent resolution of lesions thereafter. The patient was discharged with take-home medications of levocetirizine 5 mg/day tablet and betamethasone lotion applied twice daily.

DISCUSSION

Acute generalized exanthematous pustulosis is often distinguishable from other severe cutaneous adverse reactions based on the time interval between drug intake and the onset of symptoms. Typically, AGEP exhibits a relatively short time frame, with symptoms appearing within 1 to 12 days after the initial drug use. Specifically, when antibiotics are involved, the onset is usually within 1 to 2 days, compared to other medications that frequently occur between 7-12 days after drug exposure. This characteristic time interval is a key factor in differentiating AGEP from other skin reactions.[7]

The most commonly implicated agents causing AGEP include medications, such as beta-lactam antibiotics like ampicillin or amoxicillin, quinolones, antimalarials (specifically hydroxychloroquine), sulphonamides, macrolides, calcium channel blockers, and antifungal medications such as terbinafine.[5] However, AGEP from other triggers such as bacterial, viral, or parasitic infections may also occur.[6,7]

The hallmark of AGEP is the abrupt appearance of disseminated, non-follicular, small sterile pustules on a background of a confluent exanthem.[7] The lesions usually begin on the face and intertriginous areas, eventually spreading to the whole integument. Systemic manifestations may encompass symptoms such as fever, pruritus, or a sensation of burning skin. In approximately 20 to 25% of patients, there is mucosal involvement, although this is not a characteristic feature of AGEP and is usually confined to a single mucosal area, commonly affecting only the lips or buccal mucosa. In most cases, there is typically no internal organ involvement, but it may occur in some cases, specifically in the elderly population.[8] The dermatologic manifestations are commonly accompanied by systemic symptoms, primarily fever and leukocytosis, and could be linked to potential hepatic, renal, or pulmonary complications.[9,10] Blood tests may reveal an increase in lymphocytes, elevated neutrophil levels, and eosinophilia in 30% of cases.[10]

AGEP is a T cell-mediated hypersensitivity reaction classified as type IVd. The pathophysiology involves activating drug-specific CD4 and CD8 T cells, leading to the apoptosis of keratinocytes and the formation of subcorneal vesicles. These cytotoxic T cells release granzyme B and perforin, contributing to keratinocyte damage. Furthermore, drug-specific T cells in AGEP patients produce elevated levels of chemokine (C-X-C motif) ligand 8/IL-8, which is central in recruiting neutrophils and forming pustules. High levels of cytokines such as IL-17, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF) may also intensify neutrophilic activity. The release of cytokines also triggers systemic symptoms, such as fever, leukocytosis, and elevated C-reactive protein levels, as seen in our patients. Additionally, innate immune cells may play a role in the pathogenesis. Overall, the pathogenesis of AGEP involves a complex interplay of immune responses and cytokine release, resulting in the characteristic skin manifestations seen in this condition.[11,12]

Because AGEP exhibits a distinctive and rapidly evolving clinical presentation, it is primarily diagnosed based on clinical findings rather than histopathologic examination. The temporal relationship between recent drug exposure and these hallmark clinical features makes AGEP highly recognizable.[13] However, to standardize the diagnosis of AGEP, the EuroSCAR study group introduced a validated AGEP diagnostic score that relies on clinical and histological parameters. This score encompasses factors such as the appearance of skin lesions, the presence of fever, the clinical progression, and laboratory and histopathological results. It establishes a structured framework for categorizing individuals with suspected AGEP into distinct categories, including definite, probable, possible, or no AGEP, streamlining the diagnostic process for this condition.[5]

While a skin biopsy is not always necessary for the diagnosis of AGEP, it can be a useful diagnostic tool in certain cases. AGEP is typically diagnosed based on clinical criteria, including the sudden onset of pustules on an erythematous background and characteristic symptoms. However, a

skin biopsy may be recommended in cases where the diagnosis is unclear or when other skin conditions with similar symptoms need to be ruled out. A skin biopsy can provide histopathologic evidence that supports the diagnosis of AGEP. It may reveal specific features, such as intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema and both neutrophilic and eosinophilic perivascular and interstitial infiltrate, which can help confirm the diagnosis.[10] Pustular psoriasis is typically the most difficult to differentiate from AGEP. When differentiating between the two, AGEP has the above cellular infiltrates but lacks the presence of hyperplasia of the epidermis and papilloacanthosis that are classically described in psoriasis.[14] In correlation to our study, case 1 underwent a skin biopsy of the involved lesion, which showed a basketweave stratum corneum with subcorneal collections of neutrophils, lymphocytes, and histiocytes overlying a spongiotic epidermis with psoriasiform hyperplasia. The superficial dermis revealed edema and moderate to dense interstitial and perivascular inflammatory infiltrates composed predominantly of lymphocytes, histiocytes, and eosinophils. Dilated blood vessels with intraluminal eosinophils and melanophages are likewise seen. These findings were all congruent with AGEP microscopically. For cases 2 and 3, no biopsy was done; hence, they were given a score of zero (Table 2). While histopathological analysis can provide supportive evidence, it is not always specific, may vary in findings, and can introduce delays in diagnosis and treatment. Ninety percent of AGEP cases were diagnosed clinically in the study of Guzman and Paliza without the aid of a biopsy.[4]

Other ancillary procedures that can be utilized in AGEP include patch testing. The application of a drug patch test presents a valuable tool for pinpointing the culprit behind AGEP. It is advisable to conduct these assessments not earlier than 4 weeks following the resolution of AGEP symptoms but within a 12-month timeframe following the adverse reaction. A positive result frequently shows small pustules in the area of testing. The sensitivity of patch testing in diagnosing AGEP is estimated to fall within the range of 50% to 58%.[15]

In majority of cases, AGEP is linked to the use of drugs, accounting for over 90% of occurrences.[16] The drugs most significantly linked to AGEP include pristinamycin, ampicillin/amoxicillin, quinolones, hydroxychloroquine, antimicrobial sulfonamides, terbinafine, and diltiazem, as determined by a multinational case-control study conducted by EuroSCAR. Macrolides, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiepileptic medications were also noted to have weaker associations with the development of AGEP.[5] Furthermore, analgesic drugs, including tramadol, have been less frequently reported as a cause of AGEP and may also have a weaker association.[17]

Aside from drugs, other etiologic agents that were noted to be a probable cause include infection. Infectious agents like Parvovirus B19, *Chlamydia pneumoniae*, cytomegalovirus, and Coxsackie B4 have been linked to the etiology of AGEP. Recurrent urinary tract infections caused by *Escherichia coli* have also been reported as a potential cause. However, the EuroSCAR study did not find a significant risk associated with infections. Determining the association of AGEP with infections can be challenging because it is often difficult to identify the specific infectious agent, and the disease course may also be influenced by the use of antibiotics.[5,13]

As seen in Table 1, this case series presented three similar and different cases. All cases involve female patients, aged 26 - 60 years old, of Filipino ethnicity from various areas in Davao City who were unvaccinated against COVID-19 and had no history of smoking or illicit drug use. The culprit drugs in this study were all antibiotics. These findings are similar to the local study of Guzman and Paliza with antibiotics being the most common culprit.[4] As with previous studies, this case series revealed that acute generalized exanthematous pustulosis can occur in all ages with female predominance.[18] Women account for approximately 65-80% of reported cases.[18] Guzman and Paliza also reported a slight female preponderance occurring in the fourth to fifth decade of life.[4] The female predominance of AGEP may be partly due to differences in drug metabolism compared to men.[14] Although further studies should be explored to determine the association between diabetes mellitus and an increased risk of developing AGEP, several case studies have already illustrated the potential link between diabetes mellitus and the susceptibility to AGEP, likely due to a compromised immune system associated with diabetes.[19,20] Guzman and Paliza also revealed that 69% of their AGEP patients had co-morbidities, with 19% having diabetes mellitus.[4]

For patient number 1, the lesions appeared four days after the initiation of ceftriaxone. Multiple pruritic and non-follicular pustules on her back were noted initially. These lesions became generalized, involving her face, trunk, and extremities. Following the EuroSCAR scoring system, the patient scored positively for typical morphology (pustules, erythema, and distribution) and exhibited clinical course features such as fever, leukocytosis (>7000 cells), and histological evidence supporting AGEP. With that, this case is classified as "definitive AGEP" with a total score of 10. As a third-generation cephalosporin, ceftriaxone can cause immediate and delayed hypersensitivity reactions akin to penicillin. Cephalosporins distinguish themselves from penicillin through the presence of a 6-membered dihydrothiazine ring and an R2 group.[21] Some evidence suggests that the disruption of the beta-lactam ring results in the destabilization of the R2 side chain, generating unstable conjugates and poorly defined determinants.

While it's theoretically possible for IgE antibodies to bind to various parts of the beta-lactam structure, including the ring, the protein carrier molecule, and side chains, it appears that the R1 side chain and the remaining beta-lactam portion forming covalent links with host proteins play a central role in immunogenicity in the development of adverse drug reactions.[22]

For patient number 2, the patient had her first lesions 24 days after initiation of piperacillin-tazobactam and clindamycin. There was an appearance of areas of red skin studded with pinhead-sized sterile pustules over the abdomen and chest. The patient exhibited typical morphology of AGEP (pustules, erythema, and distribution), leukocytosis (>7000 cells), and fever. Hence, she scored 6 in the EuroSCAR scoring system, classified as "probable AGEP". The histological information is missing since a skin biopsy was not done on this patient, resulting in a score of zero. The culprit drug of this patient was piperacillin-tazobactam versus clindamycin. Piperacillin-tazobactam can cause AGEP through T-cell-mediated immune responses. Penicillins, including piperacillin, can covalently modify proteins to create neoantigens, which the immune system recognizes as foreign. This can lead to the activation of αβT cells, particularly CD4+ and CD8+ T cells, when they encounter these novel self-derived peptides presented by human leukocyte antigen molecules on antigen-presenting cells. This activation results in clonal expansion of T cells and the release of proinflammatory cytokines and cytotoxic molecules that directly contribute to keratinocyte apoptosis and skin lesions.[23] On the other hand, clindamycin, categorized within the lincosamide antibiotic group, primarily activates CD4 and CD8 lymphocytes, prompting the migration of T cells to the skin. These drug-specific CD8 T-cells utilize perforin, granzyme B, and Fas ligand, affecting keratinocyte apoptosis and forming epidermal vesicles. The systemic manifestations observed in AGEP may be linked to the

Table 1. Clinicodemographic profile, presentation, management, and treatment outcomes of the cases

	Case 1	Case 2	Case 3
Age/Sex	33 yo/F	60 yo/F	26 yo/F
Race	Filipino	Filipino	Filipino
Residence	Calinan, Davao City	Catalunan Grande, Davao City	Buhangin, Davao City
Comorbidities	Diabetes Mellitus Type II – Insulin Requiring	Diabetes Mellitus Type II – Insulin Requiring	Diabetes Mellitus Type II – Non Insulin Requiring
Vices	Non-smoker, non-drinker, no history of illicit drug use	Non-smoker, non-alcoholic beverage drinker, no illicit drug use	Non-smoker, occasional alcoholic beverage drinker, no illicit drug use
COVID-19 Vaccination	Unvaccinated against COVID-19	Unvaccinated against COVID-19	Unvaccinated against COVID-19
Family History of Allergic Diseases	None	None	None
Antibiotic Used	Ceftriaxone	Piperacillin Tazobactam and Clindamycin	Amoxicillin
Onset of Rashes (Post-Antibiotic Use)	4 days	24 days	1 day
Physical Examination	Numerous small, non-follicular pustules on erythematous skin involving the face, trunk, back, lower, and upper extremities, tachycardia, and tachypnea	Fluctuant mass on the posterior neck, fever, clear breath sounds, normal heart rate, slightly tachypneic, febrile, areas of red skin studded with pinhead-sized sterile pustules over the abdomen and chest	Erythematous patches on lower and upper extremities, desquamation on neck, trunk, back, warm extremities, multiple disseminated pustules on an erythematous background, fever
BMI (by Asia Pacific Classification)	21.87 kg/m^2 (Normal)	25.63 kg/m^2 (Obese I)	26.4 kg/m^2 (Obese I)
Diagnosis Based on EUROScar	Definitive AGEP	Probable AGEP	Probable AGEP
Treatment	Discontinuation of Ceftriaxone, Bilastine 20 mg/day, application of emollient and Clobetasol cream BID	Discontinuation of Piperacillin-Tazobactam and Clindamycin, Bilastine 20 mg/day, application of 1% Hydrocortisone lotion BID	Discontinuation of Amoxicillin, Levocetirizine 5 mg/day, Hydrocortisone 100 mg IV Q6H for 8 doses, application of Betamethasone lotion BID
Outcome	Resolution 5 days after discontinuation of Cetriaxone	Resolution 7 days after discontinuation of Piperacillin-Tazobactam and Clindamycin	Resolution 3 days after discontinuation of Amoxicillin

presence of circulating interleukin (IL)-17 and IL-22.[24] However, the precise mechanism behind these effects remains uncertain.

For patient number 3, pruritic erythematous flat lesions on the lower extremities manifested 24 hours after initiation of amoxicillin. The lesions progressed to involve the face and bilateral extremities, leading to generalized pustules with an erythematous base. Based on the clinical presentation and course of the disease, the EuroSCAR scoring system categorizes this case as "probable AGEP," with a total score of 6. The patient's CBC showed leukocytosis, but there was an absence of fever. The mechanism by which amoxicillin can induce AGEP is primarily attributed to the activation of CD4+ T cells in the immune response. In AGEP associated with amoxicillin exposure, CD4+ T-cell clones isolated from affected patients have been found to predominantly exhibit a Th2 cytokine profile characterized by the release of cytokines like IL-4, IL-5, and IL-13. This immune activation leads to a heterogenous immune profile with

Table 2. AGEP Diagnosis based on EuroSCAR Criteria

Parameters and scores	Case 1	Case 2	Case 3
Morphology			
Pustules Typical +2 Compatible with disease +1 Insufficient 0	+2	+2	+2
Erythema Typical +2 Compatible with disease +1 Insufficient 0	+2	+2	+1
Distribution Typical +2 Compatible with disease +1 Insufficient 0	+2	+2	+2
Score	6	6	5
Course			
Mucosal Involvement Yes -2 No 0	0	0	0
Acute Onset (<10 days) Yes 0 No -2	0	-2	0
Resolution of pustules (<15 days) Yes 0 No -2	0	0	0
Fever Yes +1 No 0	+1	+1	0
PMN (>7000 cells) Yes +1 No 0	+1	+1	+1
Histology Other diseases - 10 Not representative 0 Exocytosis of PMN cells +1 Subcorneal and/or intraepidermal non-spongiform 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	+2	None (assumed as 0)	None (assumed as 0)
Total Score (Course + Morphology)	10	6	6
Score interpretation: - 0: No AGEP; 1-4: Possible AGEP; 5-7: Probable AGEP; 8-12: Definitive AGEP.	**Definitive AGEP**	**Probable AGEP**	**Probable AGEP**

both Th1 (IFNγ, IL-2) and Th2 cytokines. Additionally, the presence of eotaxins contributes to eosinophil maturation and recruitment, consistent with AGEP pathology. CD8+ T cells, which play a role in SJS/TEN, are less prevalent in AGEP associated with AX. This highlights the pivotal role of CD4+ T cells and the immune cascade involving Th2 cytokines in the development of AGEP following exposure to Amoxicillin.[23]

The primary treatment approach for AGEP is the prompt identification and discontinuation of potential culprit drugs. Skin eruptions typically resolve within a few days following the withdrawal of these medications. Studies have reported an average duration of 6 to 7 days between pustule resolution and drug cessation.[25] First-line skin-directed therapy involves the use of potent topical steroids (applied at a rate of 20-30 grams per day until desquamation begins). If necessary, additional symptomatic relief can be provided with antipyretics. Systemic therapy with steroids is generally not required, but it may be considered in severe cases, including but not limited to cholestasis, hepatic cytolysis, nephritis, renal insufficiency, and involvement of the lungs or bone marrow, typically starting at 0.5-1 mg/kg for 2 days and then tapering over five days.[26]

In the three cases, the primary treatment approach involved discontinuing the suspected culprit drugs responsible for triggering the condition. Similar to the study conducted by Creadore et al., topical steroid applications, either alone or in combination with other treatments, were also used in this case series.[27] Hydrocortisone or betamethasone lotion was applied to affected areas to reduce inflammation. Supportive treatment was also provided for symptom management. Similar to the management done by Guzman and Paliza where 90% of patients were given systemic antihistamines,[4] the patients in this case series were also given antihistamines (bilastine or levocetirizine), for relief of pruritus. Additionally, in this case series, patients were advised to use unscented soap and practice proper daily hygiene. Desquamation and resolution of symptoms were observed within a few days to less than 2 weeks, leading to eventual discharge. This is similar to past studies that noted that AGEP usually resolves within 2 weeks with widespread superficial desquamation.[28]

Although organ involvement, mucosal involvement, subsequent infection, delayed diagnosis, and medical comorbidities may lead to a bad outcome, AGEP has a favorable prognosis. The death rate stated is 5%.[13] When death does happen, disseminated intravascular coagulation and multiple organ dysfunction are usually the causes. Following the re-exposure of the causative agent, AGEP may recur.

CONCLUSION

This case series highlights the clinical presentation, antibiotic exposure history, and treatment outcomes of three patients diagnosed with AGEP in a tertiary hospital in Davao City. The cases demonstrate the diverse clinical presentations and triggers of AGEP, primarily involving beta-lactam antibiotics such as ceftriaxone, piperacillin-tazobactam, clindamycin, and amoxicillin. The patients in this series shared some characteristics, including being female, aged between 26 and 60 years, of Filipino ethnicity, unvaccinated against COVID-19, and with no history of smoking or illicit drug use. Their AGEP diagnoses were based on clinical criteria, such as the sudden onset of pustules and erythema, typical morphology, and temporal relationship with specific medications.

This case series highlights the value of considering AGEP in the differential diagnosis of severe cutaneous reactions, particularly in patients with a recent history of antibiotic use. This case series underscores the importance of recognizing AGEP as a potential adverse reaction to antibiotics and the need for prompt identification, withdrawal of the offending medication, and timely initiation of treatment to ensure favorable outcomes. This case series emphasizes the importance of clinical expertise and diagnosis in prompt identifying AGEP, a potentially life-threatening condition, especially in countries like the Philippines, where it is underreported, to ensure timely and appropriate management.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

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REFERENCES

1. Sidoroff A. Acute generalized exanthematous pustulosis. Chem Immunol Allergy. 2012;97:139-48. PMID: 22613859 DOI: 10.1159/000335625
2. Zhang C, Van DN, Hieu C, Craig T. Drug-induced severe cutaneous adverse reactions: Determine the cause and prevention. Ann Allergy Asthma Immunol. 2019 Nov;123(5):483-7. PMID: 31400461 DOI: 10.1016/j.anai.2019.08.004. Erratum in: Ann Allergy Asthma Immunol. 2020;124(4):408. PMID: 32223944
3. Thong BY, Lucas M, Kang HR, et al. Drug hypersensitivity reactions in Asia: regional issues and challenges. Asia Pac Allergy. 2020;10(1):e8. PMID: 32099830 PMCID: PMC7016324 DOI: 10.5415/apallergy.2020.10.e8
4. Guzman AI, Paliza AC. Epidemiology of severe cutaneous adverse drug reactions in a University Hospital: a five-year review. JMUST. 2018;2(1). DOI: 10.35460/2546-1621.2017-0031
5. Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol. 2007;157(5):989-96. PMID: 17854366 DOI: 10.1111/j.1365-2133.2007.08156.x
6. Lee D, Kang JN, Hwang SH, et al. Acute generalized exanthematous pustulosis induced by parvovirus b19 infection. Ann Dermatol. 2014;26(3):399-400. PMID: 24966644 PMCID: PMC4069655 DOI: 10.5021/ad.2014.26.3.399
7. Taguchi K, Oka M, Bito T, Nishigori C. Acute generalized exanthematous pustulosis induced by Mycoplasma pneumoniae infection. J Dermatol. 2016;43(1):113-4. PMID: 26427049 DOI: 10.1111/1346-8138.13151
8. Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy. 2019;74(1):14-27. PMID: 30028512 DOI: 10.1111/all.13562
9. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute generalized exanthematous pustulosis: pathogenesis, genetic background, clinical variants and therapy. Int J Mol Sci. 2016;17(8):1214. PMID: 27472323 PMCID: PMC5000612 DOI: 10.3390/ijms17081214
10. Parisi R, Shah H, Navarini AA, et al. Acute generalized exanthematous pustulosis: clinical features, differential diagnosis, and management. Am J Clin Dermatol. 2023;24(4):557-75. PMID: 37156992 PMCID: PMC10166469 DOI: 10.1007/s40257-023-00779-3
11. Kabashima R, Sugita K, Sawada Y, Hino R, Nakamura M, Tokura Y. Increased circulating Th17 frequencies and serum IL-22 levels in patients with acute generalized exanthematous pustulosis. J Eur Acad Dermatol Venereol. 2011;25(4):485-8. PMID: 20569282 DOI: 10.1111/j.1468-3083.2010.03771.x
12. Schlapbach C, Zawodniak A, Irla N, et al. NKp46+ cells express granulysin in multiple cutaneous adverse drug reactions. Allergy. 2011;66(11):1469-76. 21819408. PMID: 21819408 DOI: 10.1111/j.1398-9995.2011.02677.x
13. De A, Das S, Sarda A, Pal D, Biswas P. Acute Generalised exanthematous pustulosis: an update. Indian J Dermatol. 2018;63(1):22-9. PMID: 29527022 PMCID: PMC5838751 DOI: 10.4103/ijd.IJD_581_17
14. Moore MJ, Sathe NC, Ganipisetti VM. Acute generalized exanthematous pustulosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2023 May 3. PMID: 37276304 Bookshelf ID: NBK592407
15. Barbaud A, Castagna J, Soria A. Skin tests in the work-up of cutaneous adverse drug reactions: a review and update. Contact Dermatitis. 2022;86(5):344-56. PMID: 35122269 DOI: 10.1111/cod.14063
16. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. J Am Acad Dermatol. 2015;73(5):843-8. PMID: 26354880 DOI: 10.1016/j.jaad.2015.07.017
17. Martinez-DelaTorre A, van Weenen, E, Kraus M, Weiler S, Feuerriegel S, Burden AM. A network analysis of drug combinations associated with acute generalized exanthematous pustulosis (AGEP). J. Clin. Med. 2021;10(19):4486. PMID: 34640505 PMCID: PMC8509508 DOI: 10.3390/jcm10194486
18. Tamir E, Wohl Y, Mashiah J, Brenner S. Acute generalized exanthematous pustulosis: a retrospective analysis showing a clear predilection for women. Skinmed. 2006;5(4):186-8. PMID: 16855410 DOI: 10.1111/j.1540-9740.2006.05019.x
19. Oh DAQ, Yeo w, Choo KJL, Pang SM, Oh CC, Lee HY. Acute generalized exanthematous pustulosis: Epidemiology, clinical course, and treatment outcomes of patients treated in an Asian academic medical center. PMID: 34409363 PMCID: PMC8362292 DOI: 10.1016/j.jdin.2020.12.004
20. Weiss M, Assier H, Hotz C, et al. Acute generalized exanthematous pustulosis: clinico-biological profile and inducing drugs in 83 patients. J Eur Acad Dermatol Venereol. 2023;37(6):e776-8. PMID: 36734481 DOI: 10.1111/jdv.18940
21. Trubiano JA, Stone CA, Grayson ML, et al. The 3 Cs of antibiotic allergy-classification, cross-reactivity, and collaboration. J Allergy Clin Immunol Pract. 2017;5(6):1532-42. PMID: 28843343 PMCID: PMC5681410 DOI: 10.1016/j.jaip.2017.06.017. Erratum in: J Allergy Clin Immunol Pract. 2018;6(1):323. Corregendum in: J Allergy Clin Immunol Pract. 2022;10(12):3346-7
22. Khan DA, Banerji A, Bernstein JA, et al. Cephalosporin allergy: current understanding and future challenges. J Allergy Clin Immunol Pract. 2019;7(7):2105-14. PMID: 31495420 PMCID: PMC6955146 DOI: 10.1016/j.jaip.2019.06.001
23. Goh SJR, Tuomisto JEE, Purcell AW, Mifsud NA, Illing PT. The complexity of T cell-mediated penicillin hypersensitivity reactions. Allergy. 2021;76(1):150-67. PMID: 32383256 DOI: 10.1111/all.14355
24. Smeets TJ, Jessurun N, Härmark L, Kardaun SH. Clindamycin-induced acute generalised exanthematous pustulosis: five cases and a review of the literature. Neth J Med. 2016 Dec;74(10):421-8. PMID: 27966434
25. Alniemi DT, Wetter DA, Bridges AG, et al. Acute generalized exanthematous pustulosis: clinical characteristics, etiologic associations, treatments, and outcomes in a series of 28 patients at Mayo Clinic, 1996-2013. Int J Dermatol. 2017;56(4):405-14. PMID: 28084022 DOI: 10.1111/ijd.13434
26. Stadler PC, Oschmann A, Kerl-French K, et al. Acute generalized exanthematous pustulosis: Clinical characteristics, pathogenesis, and management. Dermatology. 2023;239(4):328–33. PMID: 36702114 DOI: 10.1159/000529218
27. Creadore A, Desai S, Alloo A, et al. Clinical characteristics, disease course, and outcomes of patients with acute generalized exanthematous pustulosis in the US. JAMA Dermatol. 2022;158(2):176-83. PMID: 34985493 PMCID: PMC8733866 DOI: 10.1001/jamadermatol.2021.5390
28. Hotz C, Valeyrie-Allanore L, Haddad C, et al. Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients. Br J Dermatol. 2013;169(6):1223-32. PMID: 23855377 DOI: 10.1111/bjd.12502.