



Acute generalized exanthematous pustulosis: Epidemiology, clinical course, and treatment outcomes of patients treated in an Asian academic medical center

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Background: Acute generalized exanthematous pustulosis (AGEP) is a rare severe cutaneous adverse drug reaction. Although acutely patients have significant morbidity and occasional systemic involvement, the clinical course is generally self-limited. To date, there has been no consensus on treatment.

Objective: The aim of our current study was to evaluate the clinical features, drug association, treatment, and outcomes in a cohort of patients treated in an academic medical center.

Methods: A retrospective review of electronic medical records over a period of 10 years from 2009 to 2018 in a single tertiary academic medical center in Singapore was performed. Forty-three medical records with probable/definite diagnosis of AGEP were identified and analyzed for statistical significance.

Results: Drug association was identified in 93% of cases. The most frequent drug class was antibiotics, including penicillins, cephalosporins, and vancomycin. Systemic involvement was reported in 13.9% of patients. All cases of AGEP resolved with cessation of the offending drug. There was no mortality attributed to AGEP. Treatment with systemic steroid was associated with a decreased length of hospital stay ($P = .035$) in patients with AGEP.

Conclusion: AGEP was a self-limiting adverse drug reaction that was commonly caused by antibiotics. Although there was no difference in mortality, there was a significant reduction in the length of hospitalization with systemic corticosteroid treatment compared with that of topical corticosteroid treatment of AGEP. (JAAD Int 2021;3:1-6.)

Key words: AGEP; allergy; antibiotics; pustulosis; severe cutaneous adverse reaction (SCAR).

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction, characterized by an abrupt onset of non-follicular sterile pustules, with intertriginous predilection, accompanied by fever (temperature $>38^{\circ}\text{C}$) and leukocytosis. Medications are the most common

triggers and high-risk drugs include pristinamycin, quinolones, beta-lactams, calcium channel blockers, etc.¹ The latency after drug initiation has been shown to be variable, with AGEP occurring after 24–48 hours for certain classes of drugs such as penicillins and after longer lag times of 10–14 days for other high-risk drugs.¹

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Despite its acute and extensive presentation, the syndrome is typically self-resolving. Although systemic involvement has been reported in up to 20% of cases, AGEP is typically mild with a <5% mortality.²

AGEP is rare and the estimated incidence is between 1 and 5 cases per million. The current literature on its clinical features and outcomes have been largely based on limited series and anecdotal reports.³ The treatment for AGEP remains unclear, and there is limited evidence in the literature on comparisons of patient outcomes of AGEP treated with systemic and topical corticosteroids. Systemic corticosteroids are widely used for AGEP because of its florid clinical presentation, although topical corticosteroids have been advocated because of its self-limiting course.³

Our study, the largest case series in Asia to date, aimed to characterize the clinical features, risk factors, and outcomes of AGEP in an Asian Academic Medical Center and retrospectively compare the different treatment modalities and their impact on disease outcomes.

MATERIALS AND METHODS

Patient electronic medical records with the diagnosis of AGEP in an inpatient medical setting from a tertiary medical center over a 10-year period (2009-2018 inclusive) were retrospectively reviewed. Clinical data and photographs pertaining to demographics, clinical presentation, investigations, and clinical outcomes were reviewed and analyzed. In cases in which the electronic records were insufficient, physical case notes were recalled for the information required. A total of 52 cases were identified and were reviewed by a committee (Authors Oh, Yeo, Choo, and Lee). The cases were evaluated and scored in a standardized and blinded fashion according to the EuroSCAR study criteria.³ Any differences were resolved by consensus between at least 2 members. The cases were then categorized into possible AGEP cases (Score: 1-4), probable cases (Score: 5-7), or definite cases (Score: 8-12). The probable and definite cases were included for further analysis. The cases with an alternative diagnosis were excluded.

Following previously reported criteria⁴ for systemic involvement in AGEP, systemic involvement was defined as organ involvement that occurred

coincident with the onset of AGEP and could not be explained by other diagnoses. Biochemical cutoffs of aspartate aminotransferase and/or alanine aminotransferase levels of twice the upper limit of the normal range for hepatic dysfunction and serum creatinine level >1.5 times the baseline level for renal impairment were used in our study.

Data were analyzed using the statistical software IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp). The patient characteristics, comorbidities, presence of systemic involvement, treatment regimen, and outcomes (length of hospital stay and mortality) were analyzed for statistical significance. The variables were analyzed using Fisher's exact test for a sample size <5 or Wilcoxon signed-rank test for quantitative data. $P < .05$ was considered statistically significant.

CAPSULE SUMMARY

- Acute generalized exanthematous pustulosis (AGEP) is a self-limited cutaneous adverse drug reaction commonly caused by antibiotics.
- Mortality was low and independent of treatment. However, treatment of AGEP with systemic corticosteroids was associated with a reduced length of stay in our study.

data. $P < .05$ was considered statistically significant.

RESULTS

Patient characteristics

During the study period, there were 43 cases of probable/definite AGEP. The mean age of the patients was 62 years (range 23-91 years), 51.2% were female, and the ethnicities of the patients were Chinese 72.1%, Malay 16.3%, Indian 2.3%, and others 9.3%, mirroring that of Singapore's population. The clinical details are summarized in [Table I](#).

Drug associations

In 93% of cases, a suspected drug was identified. The most frequent drug classes were antibiotics such as penicillins (ampicillin, amoxicillin, and piperacillin-tazobactam), vancomycin, and cephalosporins (ceftriaxone and cefuroxime). The latency from drug initiation to the onset of symptoms was 4.5 days for antibiotics and 6.8 days for other classes of drugs. The various drug associations are summarized in [Table II](#). The remaining cases were attributed to possible viral illness ($n = 1$) and idiopathic etiology ($n = 2$).

Treatment and clinical outcomes

The median length of hospitalization was 10.0 days (25th percentile = 6.0, 75th percentile = 20.0, interquartile range = 14.0). There were 2 cases of in-hospital mortality (line sepsis and pneumonia, respectively), which were not attributed to AGEP. Out of the entire cohort of 43 cases, 6 patients

Abbreviation used:

AGEP: acute generalized exanthematous
pustulosis

(13.9%) demonstrated systemic involvement that was self-limiting. These included 2 cases (33.3%) of hepatic dysfunction and 4 cases (66.7%) of renal impairment.

Nine of the 43 patients (21%) were treated with systemic steroids. The mean dose of prednisolone was 32.2 (+/-10.0) mg/day and the mean duration of treatment was 4.4 (+/-1.1) days. The rest of the cohort was treated with topical therapy of varying potencies; 24 (70.6%) received a Group III topical steroid (betamethasone valerate 0.1% cream), 5 (14.7%) received a Group IV topical steroid (mometasone furoate 0.1% cream), and 4 (11.8%) received a Group I topical steroid (clobetasol propionate 0.05% cream). One (3.0%) patient was treated with calamine lotion only. At baseline, there were no differences in terms of the clinical characteristics and drug associations (Table III). We noted that patients with renal dysfunction were more likely to receive treatment with systemic steroids, and that the use of systemic steroids resulted in a shorter length of stay compared with that with topical steroid use. Even with the addition of the mortality cases that were not attributed to AGEP in our case series, there was no statistically significant difference in mortality between those treated with or without systemic steroids. In addition, the use of systemic steroids was not associated with an increased incidence of adverse events such as infections or deaths in our study.

DISCUSSION

In our retrospective case series, we highlighted the epidemiological factors, clinical course, and treatment methods of AGEP seen in an academic medical center in Singapore. This, to our knowledge, is the largest series of AGEP cases in Asia to date. Compared with the other case series in Asia, our patients were older (mean age 65 years), which is likely because of the aging population in Singapore. In terms of drug associations, our case study was consistent with other previously reported case series in Asia. The most frequent class of drugs responsible for AGEP in our study was antibiotics (eg, penicillins, cephalosporins, and quinolones). A significant drug cause of AGEP in our case series was vancomycin, which was reported rarely in other studies. This may reflect the increasing utilization of vancomycin because of the increased prevalence of hospital-

Table I. Patient characteristics, investigations, and other medical comorbidities

| Patient characteristics (N = 43) | N (%) |
|------------------------------------|-----------|
| Age, mean ± SD (years) | 62 ± 16 |
| Female sex, N (%) | 22 (51.2) |
| Ethnicity, N (%) | |
| Chinese | 31 (72.1) |
| Malay | 7 (16.3) |
| Indian | 1 (2.3) |
| Others* | 4 (9.3) |
| Comorbid medical conditions, N (%) | |
| Diabetes mellitus | 8 (18.6) |
| Hypertension | 24 (55.8) |
| Dyslipidemia | 20 (46.5) |
| Chronic kidney disease | 14 (32.5) |
| Ischemic heart disease | 7 (16.3) |
| Respiratory disease | 2 (4.7) |
| Neurologic disease | 10 (23.3) |
| Dermatologic disease | 4 (9.3) |
| Autoimmune disease | 1 (2.3) |
| Malignancy | 4 (9.3) |
| Hepatobiliary disease | 1 (2.3) |

SD, Standard deviation.

*Caucasian, Eurasian, Ukrainian, Pakistani.

Table II. Suspected drugs and their latency periods in our series

| Implicated antibiotics | n (%) 29 (67.4) | Latency (median 4.5 days, [IQR]) |
|------------------------------------|--------------------|-------------------------------------|
| Penicillins | 12 | 4.0 (4.5) |
| Cephalosporins | 4 | 4.5 (3.3) |
| Quinolones | 3 | 5 (3.3) |
| Vancomycin | 4 | 2.5 (24.3) |
| Other antibiotics/ antifungals* | 6 | 4.5 (3.0) |

| Other drug classes | n (%) 11 (25.6) | Latency (median 6.8 days, [IQR]) |
|--------------------------------|--------------------|-------------------------------------|
| Calcium channel blockers | 2 | 36.5 (3.0) |
| Analgesics | 3 | 6 (3.0) |
| Contrast agent (iohexol) | 2 | 1.5 (3) |
| Other medications [†] | 4 | 7.5 (5.5) |

IQR, Interquartile range.

*Other antibiotics/antifungals were clindamycin, clarithromycin, caspofungin, and ketoconazole.

[†]Other medications were levetiracetam, phenytoin, sulphasalazine, and traditional Chinese medicine.

acquired methicillin-resistant *Staphylococcus aureus*. We also identified a contrast agent (n = 2) as a possible cause of AGEP in our case series. This has not been reported in other studies except in a Korean study,⁵ suggesting that future studies are required to examine drug associations and AGEP in Asians.

Table III. Comparison of patient characteristics, implicated drugs, and outcomes between patients treated with systemic and topical corticosteroids

| Baseline characteristics comorbidities | Systemic corticosteroids (n = 9) | Topical corticosteroids (n = 34) | P value |
|--|----------------------------------|----------------------------------|---------|
| Age, mean \pm SD, years | 57.6 (\pm 22.6) | 64.1 (\pm 14.4) | .157 |
| Male sex | 4 | 16 | .204 |
| Diabetes mellitus | 0 | 8 | .220 |
| Hypertension | 3 | 21 | .264 |
| Hyperlipidemia | 3 | 17 | .076 |
| Chronic kidney disease | 1 | 14 | .025 |
| Ischemic heart disease | 2 | 5 | .414 |
| Hepatobiliary | 1 | 0 | .524 |
| Dermatologic history | 1 | 3 | .445 |
| Malignancy | 0 | 4 | .380 |
| Implicated drugs | | | |
| Penicillins | 1 | 12 | .076 |
| Cephalosporins | 0 | 5 | .344 |
| Quinolones | 2 | 2 | .500 |
| Macrolide | 1 | 0 | .524 |
| Clindamycin | 1 | 2 | .473 |
| Vancomycin | 2 | 2 | .500 |
| Other antibiotics | 0 | 2 | .445 |
| Calcium channel blockers | 0 | 2 | .445 |
| Antifungals | 0 | 2 | .445 |
| Analgesics | 1 | 2 | .473 |
| Contrast agent | 0 | 2 | .445 |
| Other medications | 0 | 2 | .445 |
| Systemic involvement | | | |
| Elevated transaminases | 0 | 2 | .810 |
| Renal impairment | 3 | 1 | .026 |
| Outcomes | | | |
| Median LOS in days (IQR) | 6.0 (5.0- 9.0) | 10.0 (6.2-31.5) | .035 |
| Mortality | 0 | 2 | .445 |

CI, Confidence interval, IQR, interquartile range; LOS, length of stay; RR, relative risk; SD, standard deviation.

Similar to previous studies,⁶ 2 distinct patterns of latency were seen: a shorter latency in antibiotic-related AGEP and a longer latency for non-antibiotics. Reasons for this remain unclear; possibilities include prior sensitization to antibiotics and/or the role of infections as a cofactor in triggering the drug reaction.

AGEP with systemic involvement has been reported in the literature and our findings corroborate those of Hotz et al,⁴ suggesting that this is not uncommon, ranging from 14% to 28%. Nonetheless, they were generally self-resolving. This is distinct from systemic involvement in other severe cutaneous adverse reactions such as drug rash with eosinophilia and systemic symptoms and Stevens-Johnson syndrome/toxic epidermal necrolysis. In addition, our study showed that the mortality rate in AGEP is low even though AGEP is often classified as a severe cutaneous adverse reaction, alongside diseases such as drug rash with

eosinophilia and systemic symptoms and Stevens-Johnson syndrome/toxic epidermal necrolysis.

Currently, there is no consensus on the treatment of AGEP. The self-limiting disease course led some to suggest that topical potent corticosteroids are sufficient, although systemic corticosteroids remain widely prescribed (Table III). Our data suggests that there was no mortality difference between those treated systemically versus those treated locally, although systemic therapy might be associated with a shorter length of stay. There were inherent flaws in our study. The sample size was small and the event rate of mortality was very low. The study was a noncontrolled, retrospective study conducted in a reference center setting, raising the possibility of selection and referral bias.

In summary, our series showed that AGEP is a self-limited condition and similar drug causality exists between Asian and other ethnicities (Table IV). Our preliminary data suggested that the use of systemic

Table IV. Summary of published case series of AGEP*

| Study | Country | No. of patients | Etiology, commonly implicated drugs (No. of patients) | Latency (Median) | Systemic involvement (No. of patients) | Treatment (No. of patients) | Outcomes |
|--------------------------------------|-----------|-----------------|--|------------------|---|--|------------------------------------|
| Current study | Singapore | 43 | Drugs (40) Top 3 drugs: penicillin (12), cephalosporin (4), vancomycin (4) Unknown (3) | 4.5 | Hepatocellular (2) Renal (4) | Withdrawal of drug, topical steroids (34), systemic corticosteroids (9) | Resolution of AGEP in all patients |
| Siew et al ⁷ (2018) | Malaysia | 21 | Drugs (21) Top 3 drugs: amoxicillin (10), cloxacillin (3), phenytoin (2) | 3.0 | Hepatocellular (3) | Withdrawal of drug, topical steroids (11), systemic corticosteroids (1), antihistamines (6) | Resolution of AGEP in all patients |
| Alniemi et al ⁸ (2017) | USA | 28 | Drugs (26) Top 3 drugs: clindamycin (6), amoxicillin (3), cephalexin (2), cefepime (2), diltiazem (2) Unknown (2) | 8.3 | Hepatocellular (19), Renal (9), Pulmonary (7), Hemodynamic instability (2) | Withdrawal of drug (23), systemic corticosteroids (11), topical therapies (26), antihistamines (14) | Resolution of AGEP in all patients |
| Thienvibul et al ⁹ (2015) | Thailand | 19 | Drugs (18) Top 3 drugs: neta-lactams (8), carbapenem (3), cephalosporin (3) Viral infection (1) | 3.0 | Hepatocellular (5) | Topical corticosteroid (11), oral prednisolone (6), supportive care (2) | Resolution of AGEP in all patients |
| Hotz et al ⁴ (2013) | France | 58 | Drugs (57) Top 3 drugs: amoxicillin (11), amoxicillin-clavulanic acid (3), pristinamycin (8) Unknown (1) | 4.5 | Renal (6), Hepatocellular (7), Pulmonary (2), Bone marrow (1) | Withdrawal of drug, topical corticosteroids (58). No systemic corticosteroid used. | Resolution of AGEP in all patients |
| Choi et al ⁵ (2010) | Korea | 36 | Drug (23) Top 3 drugs: amoxicillin (6), herbal medicine (4), lacquer (3), iopamidol (2) Unknown (13) | 9.5 | NA | Oral or intravenous steroid (24), oral antihistamines (9), topical steroids (1) 2 patients were not treated | Resolution of AGEP in all patients |
| Chang et al ¹⁰ (2008) | Taiwan | 16 | Drug (10) Top 3 drugs: beta-lactams (5), antiepileptics (2), quinolones (2) Infection (4), contact history with scabies (1), unknown (1) | 2.7 | NA | IV hydrocortisone (8), topical corticosteroids (2), oral corticosteroid (5), antihistamine (1) | Resolution of AGEP in all patients |

Continued

Table IV. Cont'd

| Study | Country | No. of patients | Etiology, commonly implicated drugs (No. of patients) | Latency (Median) | Systemic involvement (No. of patients) | Treatment (No. of patients) | Outcomes |
|------------------------------------|---------------|-----------------|--|------------------|--|-----------------------------|------------------------------------|
| Sidoroff et al (2007) ¹ | Multinational | 97 | Drugs (97) Top 3 drugs: pristinamycin (10), aminopenicillins (18), quinolones (9) | NR | NR | NR | NR |
| Roujeau et al (1991) ⁶ | France | 63 | Drugs (55): Top 3 drugs: amoxicillin (18), ampicillin (5), pristinamycin (4), Mercury (8), viral infection (4), Unknown (3) | 5 | Renal (15) | NR | Resolution of AGEP in all patients |

AGEP, Acute generalized exanthematous pustulosis; IV, intravenous; NR, not reported.

*Restricted to case series with a sample size >10.

corticosteroids may be associated with a reduced length of stay; our data is underpowered to fully evaluate differences in the mortality rate between groups, and further studies may be warranted.

Conflicts of interest

None disclosed.

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