

***no patient handout*

Acute generalized exanthematous pustulosis

Synopsis

Acute generalized exanthematous pustulosis (AGEP) is a relatively rare reaction pattern consisting of an acute febrile pustular eruption following medications, mercury exposure, or viral infection (enterovirus, adenovirus, cytomegalovirus [CMV], Epstein-Barr virus [EBV], hepatitis B). The syndrome occurs within 2 weeks of starting the medication and may occur as soon as 48 hours after initial drug ingestion. AGEP has been reported in infants, children, and adults. Fever, typically 39°C (102.2°F), is a near constant feature and persists about 1 week.

The causative drugs are primarily antibiotics, typically penicillins, and macrolides, but many other drug culprits have been reported, including norfloxacin, diltiazem, nitrazepam, cephadrine, doxycycline, vancomycin, isoniazid, carbamazepine, nifedipine, acetaminophen, quinidine, itraconazole, piperazine, ibuprofen, and pyrimethamine.

Codes

ICD10CM:

L27.0 – Generalized skin eruption due to drugs and medicaments taken internally

SNOMEDCT:

238996003 – Drug-induced toxic pustuloderma

Look For

Numerous small nonfollicular pustules develop on erythematous and edematous plaques. Burning and pruritus are frequent complaints. Pustules can begin on face or intertriginous areas. Lesions become widespread within a few hours. Palms and soles are usually not involved. Facial edema occurs in one-third of patients. Mucous membrane involvement with erosions of the mouth, lips, and tongue occur in around one-fifth of patients. Rarely, localized targetoid lesions, bullae, or intraoral pustules are seen. Internal organ involvement is not a feature. Spontaneous healing occurs within 2 weeks, and then desquamation, with collarettes of scale, for several days is usual.

Diagnostic Pearls

Acute onset of fever and erythematous eruption studded with tiny pustules (median 1 day) in association with marked neutrophilia.

Differential Diagnosis & Pitfalls

- **Pustular psoriasis** has associated arthritis and lacks the acuteness of drug association.
- **Drug hypersensitivity syndrome** – Pustules have rarely been reported in this setting. Consider this diagnosis, especially in a patient with facial edema, lymphadenopathy, and atypical lymphocytes on peripheral smear.

- **Toxic epidermal necrolysis** – Bullae and targetoid lesions have rarely been reported in AGEP in association with the more typical clinical findings outlined above. In AGEP, full-thickness necrosis of epidermis and widespread denudation do not occur.
- **Exanthematous drug eruption**
- **Viral exanthem**
- **Folliculitis**
- **Cutaneous candidiasis**
- **Miliaria pustulosa**

Best Tests

CBC shows moderate leukocytosis and marked neutrophilia.

Hypocalcemia related to hypoalbuminemia.

Culture of pustules is usually sterile, but one-third are positive, usually for *Staphylococcus aureus*, denoting secondary infection.

Skin biopsy can be diagnostic:

- Pustules may be intracorneal, subcorneal and intraepidermal in location
- Intraepidermal pustules are spongiform in appearance
- Pustules contain neutrophils and may contain eosinophils
- Other epidermal findings: spongiosis, neutrophil exocytosis
- Dermal findings include papillary dermal edema and a mixed infiltrate including neutrophils and eosinophils

Management Pearls

A thorough history looking for potential inciting drug causes, other ingestants, exposures or infections should be sought.

Discontinue any potential drug culprits promptly.

Spontaneous resolution usually occurs within 2 weeks.

Therapy

This section discusses treatment in adults.

Treatment is symptomatic. Antipyretics can be administered for fever. A class 1 or 2 topical corticosteroid can be used to relieve pruritus. A cream preparation is preferred for broad areas of involvement. If the face or folds are involved, choose a class 6 or 7 topical corticosteroid for these areas.

High-potency topical corticosteroids (class 1-2):

- Fluocinonide cream – Apply every 12 hours, or
- Desoximetasone cream – Apply every 12 hours, or
- Clobetasol cream – Apply every 12 hours, or
- Betamethasone dipropionate cream – Apply every 12 hours.

Low-potency topical corticosteroids (class 6-7):

- Hydrocortisone 2.5% cream or desonide cream applied to lesions every 12 hours.

Consider the use of oral prednisone 1 mg/kg/day (taper over 2 weeks) or intravenous methylprednisolone in widespread or otherwise severe cases.

Antihistamines can be used adjunctively for pruritus. Look for and treat bacterial superinfection.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
5 alpha-reductase inhibitor	1
5-aminosalicylic acid derivative	1
acarbose	2

Medication	Citations
acenocoumarol	<u>1</u>
acetaminophen	<u>6</u>
Acetylcholinesterase inhibitor	<u>1</u>
aldesleukin	<u>1</u>
allopurinol	<u>2</u>
Alpha-adrenergic antagonists	<u>2</u>
aminoglycoside	<u>1</u>
amoxapine	<u>2</u>
amoxicillin	<u>13</u>
amoxicillin + clavulanic acid	<u>8</u>
amphotericin B	<u>1</u>
ampicillin	<u>4</u>
Antiarrhythmic	<u>2</u>

Medication	Citations
Antibiotic	<u>3</u>
Anticoagulant	<u>2</u>
Anticonvulsant	<u>11</u>
Antidiabetic	<u>2</u>
Antifungal	<u>27</u>
Antigout	<u>2</u>
Antihistamine	<u>5</u>
Antimalarials	<u>12</u>
Antimetabolite	<u>1</u>
Antimicrobial	<u>6</u>
Antimycobacterial	<u>3</u>
Antineoplastic antibiotic	<u>2</u>
Antineoplastic antimicrotubular	<u>2</u>

Medication	Citations
Antiparasitic	<u>1</u>
Antipsychotic	<u>1</u>
aspirin	<u>1</u>
Atypical antipsychotic	<u>2</u>
azathioprine	<u>2</u>
azithromycin	<u>2</u>
BCR-ABL tyrosine kinase inhibitor	<u>5</u>
benzocaine	<u>1</u>
benzodiazepine	<u>1</u>
Beta blockers	<u>1</u>
Beta-lactam antibiotic	<u>8</u>
bleomycin	<u>1</u>
budesonide	<u>1</u>

Medication	Citations
bupropion	<u>1</u>
Calcium channel blocker	<u>13</u>
carbamazepine	<u>4</u>
cefaclor	<u>3</u>
cefadroxil	<u>1</u>
cefepime	<u>1</u>
cefotaxime	<u>1</u>
cefprozil	<u>1</u>
ceftazidime	<u>1</u>
ceftibuten	<u>1</u>
ceftriaxone	<u>6</u>
celecoxib	<u>7</u>
cephalexin	<u>2</u>

Medication	Citations
cephalosporin	<u>17</u>
cephradine	<u>1</u>
cetirizine	<u>1</u>
chloroquine	<u>1</u>
ciprofloxacin	<u>4</u>
clindamycin	<u>6</u>
clopidogrel	<u>3</u>
cloxacillin	<u>2</u>
cocaine	<u>1</u>
Corticosteroid	<u>5</u>
cytarabine	<u>1</u>
dalteparin	<u>1</u>
dapson	<u>1</u>

Medication	Citations
daptomycin	<u>2</u>
dexamethasone	<u>2</u>
dextromethorphan	<u>1</u>
diltiazem	<u>12</u>
diphenhydramine	<u>1</u>
dipyron	<u>1</u>
Diuretic	<u>3</u>
docetaxel	<u>2</u>
doxycycline	<u>1</u>
enzalutamide	<u>1</u>
erlotinib	<u>1</u>
ertapenem	<u>1</u>
erythromycin	<u>2</u>

Medication	Citations
etanercept	<u>1</u>
etodolac	<u>1</u>
famotidine	<u>1</u>
fenofibrate	<u>1</u>
fexofenadine	<u>1</u>
finasteride	<u>1</u>
fluconazole	<u>2</u>
fluoroquinolone	<u>7</u>
furosemide	<u>2</u>
gadolinium	<u>1</u>
galantamine	<u>2</u>
gefitinib	<u>1</u>
gentamicin	<u>1</u>

Medication	Citations
Glycopeptides	<u>5</u>
Histamine H1 antagonist	<u>5</u>
Histamine H2 antagonist	<u>3</u>
hydrochlorothiazide	<u>1</u>
hydroxychloroquine	<u>13</u>
hydroxyzine	<u>3</u>
ibrutinib	<u>1</u>
ibuprofen	<u>5</u>
icodextrin	<u>3</u>
imatinib	<u>5</u>
infliximab	<u>1</u>
ipilimumab	<u>1</u>
isoniazid	<u>2</u>

Medication	Citations
Isotretinoin	<u>1</u>
itraconazole	<u>3</u>
iv immune globulin	<u>1</u>
ketoconazole	<u>1</u>
labetalol	<u>1</u>
lansoprazole	<u>1</u>
lapatinib	<u>1</u>
Laxative	<u>2</u>
Leprostatic	<u>1</u>
levetiracetam	<u>2</u>
levofloxacin	<u>2</u>
lincomycin	<u>2</u>
Lincosamides	<u>7</u>

Medication	Citations
Local anesthetic	<u>1</u>
lopinavir	<u>2</u>
low molecular weight heparin	<u>1</u>
macrolide	<u>4</u>
meropenem	<u>2</u>
methimazole	<u>1</u>
methylphenidate	<u>1</u>
methylprednisolone	<u>1</u>
mifepristone	<u>1</u>
minocycline	<u>1</u>
Monoclonal antibody	<u>2</u>
morphine	<u>3</u>
moxifloxacin	<u>3</u>

Medication	Citations
naproxen	<u>1</u>
nifedipine	<u>1</u>
nimesulide	<u>1</u>
norfloxacin	<u>1</u>
NRTI antiretroviral	<u>1</u>
NSAID	<u>14</u>
nystatin	<u>4</u>
olanzapine	<u>1</u>
omeprazole	<u>2</u>
Opioid analgesic	<u>6</u>
paroxetine	<u>1</u>
penicillin antibiotic class	<u>20</u>
pentoxifylline	<u>1</u>

Medication	Citations
phenylbutazone	<u>1</u>
phenytoin	<u>5</u>
piperacillin	<u>3</u>
piperacillin + tazobactam	<u>2</u>
piroxicam	<u>2</u>
prednisolone	<u>5</u>
pristinamycin	<u>7</u>
progesterone	<u>1</u>
propafenone	<u>1</u>
propoxyphene	<u>1</u>
protease inhibitors	<u>2</u>
Proton pump inhibitor	<u>3</u>
pseudoephedrine	<u>5</u>

Medication	Citations
quetiapine	<u>1</u>
quinidine	<u>1</u>
ranibizumab	<u>1</u>
ranitidine	<u>2</u>
Retinoid	<u>1</u>
rifabutin	<u>1</u>
rifampin	<u>1</u>
ritodrine	<u>1</u>
ritonavir	<u>1</u>
rivaroxaban	<u>1</u>
Salicylates	<u>1</u>
Selective serotonin reuptake inhibitor	<u>3</u>
sennoside	<u>2</u>

Medication	Citations
sertraline	<u>2</u>
simvastatin	<u>2</u>
sorafenib	<u>4</u>
statin	<u>2</u>
sulfamethoxazole	<u>1</u>
sulfamethoxazole + trimethoprim	<u>2</u>
sulfasalazine	<u>1</u>
sulfonamide	<u>3</u>
telavancin	<u>1</u>
terazosin	<u>2</u>
terbinafine	<u>20</u>
tetracycline antibiotic class	<u>3</u>
tetrazepam	<u>1</u>

Medication	Citations
ticagrelor	<u>1</u>
ticlopidine	<u>1</u>
tigecycline	<u>1</u>
tocilizumab	<u>1</u>
Tricyclic antidepressant	<u>2</u>
Tyrosine kinase inhibitor	<u>7</u>
valdecoxib	<u>2</u>
vancomycin	<u>4</u>
varenicline	<u>3</u>
zidovudine	<u>1</u>