

# Severe Cutaneous Adverse Reactions: Acute Generalized Exanthematous Pustulosis, Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

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## KEYWORDS

- Acute generalized exanthematous pustulosis
- Stevens-Johnson syndrome • Toxic epidermal necrolysis
- Intravenous immunoglobulins

Most drug hypersensitivity reactions show skin symptoms. The most severe cutaneous manifestations include pustular and bullous skin eruptions. These 2 manifestations can lead to acute generalized exanthematous pustulosis (AGEP), or Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These are rare complications, but should be known to any doctor prescribing drugs because they are life threatening, and early stoppage of treatment is mandatory.

## ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

### *Definition*

AGEP is an acute febrile, generalized rash, with small uniform noninfective, nonfollicular associated pustules, with a tendency for the skin manifestation to be accentuated in the intertriginous and flexural regions and a predilection for females. In the vast majority of cases, AGEP is induced by drugs, mainly by anti-infectives (antibiotics,

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antimalarials, and antifungals). The term AGEP was instituted for the first time in 1980 by Beylot and colleagues,<sup>1</sup> but in the late 1960s a handful of cases atypical for psoriasis had already been described within a large case series of patients with pustular psoriasis.<sup>2</sup>

### ***Clinical Background***

AGEP manifests itself within days after the onset of a generalized rash, with nonfollicular associated small uniform pustules on an initially unaffected skin. The intertriginous and flexural parts are particularly affected, leading to discussion with protagonists arguing that AGEP and symmetric drug-related intertriginous and flexural exanthema (systemic drug-related intertriginous and flexural exanthema, Baboon syndrome) might be of the same entity, but with differential manifestation. The manifestation of AGEP very often includes, besides the trunk and extremities, the face in many cases, whereas typically the mucosal membranes (mouth, conjunctivae, genitals) and the palmoplantar surfaces are spared. In almost all cases there are fever and neutrophilia in the peripheral blood, but eosinophilia in the peripheral blood is only seen occasionally. Internal organ involvement is not a typical feature of AGEP. The duration of the rash without therapy is 7 to 21 days (Fig. 1).

### ***Differential Diagnoses***

The following diseases should be considered: generalized pustular psoriasis (Zumbusch psoriasis), subcorneal pustulosis (Sneddon-Wilkinson disease), subcorneal immunoglobulin A (IgA) dermatosis, infectious folliculitis, viral exanthema with secondary postulation, and Sweet syndrome (neutrophilic dermatosis of the skin).

Generalized pustular psoriasis (Zumbusch psoriasis) is where pustules typically manifest themselves often on lesioned skin, with polyarthritis and palmoplantar involvement. In addition, a positive family history for psoriasis usually exists, and relapses of generalized pustulation occur often.

Subcorneal pustulosis (Sneddon-Wilkinson disease) and subcorneal IgA dermatosis often present with similar clinical features to the aforementioned disease, but sometimes mucosal involvement is seen, and only diagnostic procedures such as a skin biopsy can distinguish the diseases.

Infectious folliculitis is always a major differential diagnosis of AGEP although the typical manifestations are follicular-associated abscesses of bacterial, fungal, or viral pathogens. Unfortunately, a follicular or a nonfollicular association of pustulosis cannot always be made on a macroscopic observation.

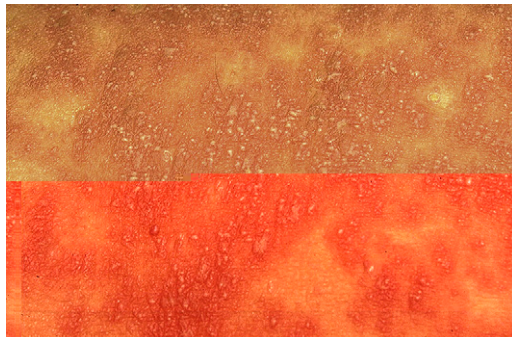


**Fig. 1.** Acute generalized exanthematous pustulosis.

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stimulation tests to identify drug-specific T cells, either indirectly with positive delayed-type hypersensitivity by patch tests or by proliferation of T cells or interferon- $\gamma$  release ex vivo by specific T cells. Patch testing to identify the culprit drug has an intermediate sensitivity, but importantly, besides a readout after 48 and 72 hours, another readout should be performed at either 96 or 120 hours to increase the sensitivity. Not uncommonly, pustule formation, like in acute AGEF, can be seen at the test site. The test should be as early as 1 month after disease resolution. The possibility of induction of AGEF due to patch testing is generally considered to be low. As a further tool besides patch tests, LTT or interferon- $\gamma$  release tests can be performed in the case of negative or unclear patch tests to increase the sensitivity of diagnostic procedures.<sup>5,12</sup> It has to be kept in mind, however, that these tests should be only performed in specialized laboratories having a strong experience in drug testing, because of the difficulty of reliably performing these tests and interpreting them. After having identified the culprit drug or in case of negative patch tests or ex vivo tests, patients should be always given a document clearly indicating the possible culprit drug or drugs, and potential cross-reactive molecules to reduce risks of a further episode of AGEF.

### **Demography**

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Studies including patients in Europe, Israel, and South-East Asia show a tendency of AGEF to be more frequent in females than in males, whereas a single study in Mexico with 12 patients revealed a slight male predominance (7 of 12 patients).<sup>4,7,13,14</sup> The mean age of development of AGEF in the EuroSCAR study (Austria, France, Israel, Italy, the Netherlands, and Germany) was 56 years and in the smaller study from Mexico, 28 years. The overall frequency of AGEF is reported in one article as being up to 5 cases per million inhabitants annually,<sup>8</sup> but is probably higher due to lack of correct workup in patients with pustulosis. Genetic associations are discussed, but clear-cut evidence is missing at the moment.

### **Etiology**

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In most AGEF cases, drugs and especially anti-infectives have been identified as the cause of the disease. Some cases make a direct link to systemic mercury exposure days before the onset of AGEF.<sup>15</sup> A case report series of AGEF was reported as a consequence of spider bites.<sup>16</sup>

The EuroSCAR study has identified pristinamycin (macrolide), ampicillin/amoxicillin, quinolones, aromatic sulfonamides, (hydroxy-)chloroquine, terbinafine, and diltiazem.<sup>7</sup> Other less strong associations were made with corticosteroids, macrolides other than pristinamycin, nonsteroidal anti-inflammatory drug (NSAID) of oxican type, and antiepileptic drugs (with the exception of valproic acid). No association was found with paracetamol (acetaminophen), benzodiazepine, angiotensin-converting inhibitors,  $\beta$ -blockers, calcium channel blockers (with the exception of diltiazem), sartanes, allopurinol, and cephalosporins, which are typical inducers of SJS/TEN. Furthermore, in the EuroSCAR study and in other studies, no pathogenetic link to pustular psoriasis was observed. In addition, human immunodeficiency virus (HIV) drugs such as nevirapine seem not to be associated with an elevated risk of inducing AGEF, contrary to the increased risk for SJS and TEN.

In a Mexican study, similar drugs causing AGEF were identified, as well as 2 cases in which cephalosporin was found to be the cause.<sup>4</sup> The interval between drug intake and the onset of AGEF can be generally divided into groups of 5 days or less of intake and 22 days or less of intake. Typically anti-infectious drugs (pristinamycin, aminopenicillin, quinolones, and anti-infective sulfonamides) lead to development of rash

within 5 days, whereas chloroquine, diltiazem, terbinafine, and hydroxychloroquine tend to lead to delayed induction of rash (Box 2).<sup>3,4,6,7</sup>

### **Therapy**

There is an absolute necessity to establish a correct diagnosis and to rule out any infectious disease before administering intermediate to high doses of systemic corticosteroids over several days. In addition, local corticosteroids of high potency (class I and class II) can be applied for 5 to 10 days.

## **STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS**

### **Definition and Historical Background**

SJS was first described in 1922, as an acute mucocutaneous syndrome in 2 young boys. The condition was characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and “erythema multiforme-like” cutaneous lesions. It was later termed Stevens-Johnson syndrome, defined as a severe mucocutaneous disease with a prolonged course and a potentially lethal outcome that is in most cases drug-induced, and should be distinguished from erythema multiforme major (EMM).<sup>17,18</sup>

In 1956, Lyell<sup>18</sup> described 4 patients with an eruption resembling scalding of the skin, which he called toxic epidermal necrolysis. It was only as more patients with TEN were reported in the years after his original publication that it became clear that TEN was drug induced. Nowadays, SJS and TEN are considered to be 2 ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by the extent of skin detachment.

### **Epidemiology**

SJS and TEN are rare diseases. The incidence of TEN is 1.89 cases per million inhabitants per year, as reported for Western Germany and Berlin in 1996,<sup>19</sup> with similar frequencies in the United States.<sup>20,21</sup> Regional differences in drug prescription, genetic background (HLA, metabolizing enzymes) of patients, and coexisting diseases including infectious diseases (HIV, tuberculosis), cancer, and radiotherapy<sup>22,23</sup> probably have an impact on the actual incidence of SJS and TEN.

### **Etiology and Pathogenesis**

#### **Genetic susceptibility**

To identify genetic factors associated with drug hypersensitivity, populations with various ethnic backgrounds were studied. A unique and strong association among

#### **Box 2**

##### **Drugs with high risk for induction of AGEF (EuroSCAR)**

Pristinamycin

Ampicillin/amoxicillin

Quinolone

Hydroxychloroquine

Terbinafine

Diltiazem

Anti-infective sulfonamides

HLA, drug hypersensitivity, and ethnic background was described by Chung and colleagues,<sup>24</sup>

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### ***Late phase and sequelae***

Sequelae are common features of late-phase TEN (75% of all cases) with typical manifestations including hyper- and hypopigmentation (62.5%), nail dystrophies (37.5%), conjunctival keratinization (62.5%), and keratoconjunctivitis sicca (50%).

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apoptosis followed by necrosis is the pathogenic basis of the widespread



Not only the type of drug but also the duration of drug intake is a potential risk factor. Drugs with an intake of less than 8 weeks induce severe drug reactions significantly more often (Table 2).<sup>19,41</sup>

**Diagnosis and Diagnostic Methods**

After an initial clinical judgment and evaluation of the extent of skin and mucosal involvement, a skin biopsy has to be performed as soon as possible. Cryosection stains are available within 1 hour after biopsy and show large numbers of necrotic keratinocytes, skin detachment of the basal epidermal layer, and no intraepidermal clefting.

An additional histologic workup with formaldehyde-fixed paraffin slides, conventional staining, and direct immune fluorescence should be done to definitively confirm the initial cryosection-based histologic diagnosis and to rule out autoimmune blistering diseases.

**Management and Therapy**

**Treatment in the acute stage**

**Prompt withdrawal of culprit drugs and supportive care** Garcia-Doval and colleagues<sup>42</sup> have shown that the earlier the causative drug is withdrawn, the better the prognosis, and that patients exposed to causative drugs with long half-lives have an increased risk of dying.

SJS and TEN are life-threatening conditions, and therefore supportive care is an essential part of the therapeutic approach. A multicenter study conducted in the United States and a smaller study showed a positive correlation of early referral to specialized intensive care units such as burn units, and survival.<sup>33,43</sup>

Wounds should be treated conservatively, with nonadhesive wound dressings being used where required. Topical sulfa-containing medications should be avoided.

**Drug therapy** To date, specific therapy for SJS and TEN, which has shown efficacy in controlled clinical trials, does not exist.

**High-dose intravenous immunoglobulins** As a consequence of the discovery of the anti-Fas potential of pooled human intravenous immunoglobulins (IVIG) in vitro,<sup>35</sup> IVIG have been tested for the treatment of TEN, and their effect reported in different noncontrolled studies. To date numerous case reports and 11 noncontrolled clinical studies containing 10 or more patients have analyzed the therapeutic effect of IVIG in TEN. All except 1 study<sup>44</sup> confirm the known excellent tolerability and a low toxic potential of IVIG when used with appropriate precaution in patients with potential risk factors (renal insufficiency, cardiac insufficiency, IgA deficiency, thromboembolic risk).<sup>45</sup>

Taken together, although each study has its potential bias and the 11 studies are not directly comparable, 8 of the 11 studies suggest that there may be a benefit of IVIG used at total doses greater than 2 g/kg over 3 to 4 days on the mortality associated with TEN.<sup>35,44,46–53</sup> Given that in certain studies the early administration of IVIG in

| Table 2<br>Drugs with high risk of inducing SJS/TEN |                 |               |              |               |
|-----------------------------------------------------|-----------------|---------------|--------------|---------------|
| Selected Drugs with Increased Risk                  |                 |               |              |               |
| TMP/SMX                                             | Aminopenicillin | Cephalosporin | Quinolone    | Carbamazepine |
| Phenytoin                                           | Phenobarbital   | Nevirapine    | Oxicam-NSAID | Allopurinol   |

TEN has shown the potential to reduce mortality, and given the favorable side effect profile of IVIG and the absence of any other clinically proven specific therapeutic alternative, early administration of high-dose immunoglobulin should, in the authors' opinion, be considered in severe forms of TEN.

The concomitant administration of corticosteroids or immunosuppressive agents remains controversial. Only 1 cycle of IVIG treatment administered over a period of 3 to 5 days is usually required in this condition. The dose recommended in TEN differs from that in other autoimmune diseases. A total dose of 3 g/kg body weight is generally recommended. IVIG has also been applied in a few children with SJS/TEN. The incidence of SJS and TEN is lower in children than in adults, but 2 studies point toward a beneficial trend for the use of IVIG.<sup>54,55</sup>

Clinical data are currently insufficient to draw conclusions on the therapeutic efficacy of IVIG in TEN. A multicenter, comparative analysis needs to be performed to determine the role of IVIG in the management of patients with SJS and TEN.

Cyclosporin A (CsA), a calcineurin inhibitor, is an efficient drug in transplantation and autoimmune diseases. Clinical data are currently insufficient to draw conclusions on the therapeutic potential of CsA, also in combination with other drugs, in TEN.<sup>56,57</sup>

Special attention has to be paid to the prevention of ocular complications. Early referral to an ophthalmologist is mandatory for assessment of the extent of eye involvement and prompt treatment with topical steroids. Some of the ocular complications have an inflammatory background, and have to be treated occasionally with ophthalmic steroids and/or extensive lubrication of the eye to prevent progression leading ultimately to the need for corneal transplantation.<sup>58</sup> Visual outcome is reported to be significantly better in patients who receive specific ophthalmologic treatment during the first week of disease.<sup>59</sup>

Systemic steroids were the standard treatment until the early 1990s, although no benefit has been proved in controlled trials, and their use therefore remains controversial. A recent small retrospective monocenter study suggests, however, that a short-course "pulse" of high-dose corticosteroids (dexamethasone) may be of benefit.<sup>60</sup>

Other anti-inflammatory therapies, such as tumor necrosis factor- $\alpha$  inhibitors, were administered in single cases with partial positive effects, but at the moment these medications are not regular therapeutic options. The potential side effect of these drugs with potential enhancement of immunosuppression and consequent increased risk of sepsis should always be taken into consideration.

### **Allergological Testing**

The severity of SJS and TEN does not allow rechallenges or intradermal tests with the culprit drugs because of the risk of inducing a second episode of SJS/TEN. Patch testing is under discussion but is not a regular diagnostic option at the moment. Only one study with patch testing in patients with SJS/TEN has been conducted in recent years. Wolkenstein and colleagues<sup>61</sup> performed patch testing in 22 suspected SJS/TEN patients. Only 2 out of 22 tested patients had a relevant positive test, suggesting a weak sensitivity in SJS and TEN.

The focus currently lies on ex vivo or in vitro tests. The LTT is an ex vivo method established in delayed drug hypersensitivity. The LTT measures the proliferation of T cells to a drug in vitro by generating T-lymphocyte cell lines and clones. Pichler and Tilch<sup>12</sup> report a sensitivity of 60% to 70% for patients allergic to  $\beta$ -lactam antibiotics in classic exanthematic drug rash. Unfortunately, the sensitivity of LTT is still very low in SJS and TEN. To improve the sensitivity in SJS and TEN, LTT should be done within 1 week after onset of the disease to get the highest (but in respect of all cases, still low) sensitivity.<sup>62</sup>

Novel in vitro methods to identify drug-specific T lymphocytes are a necessity. A new drug-specific cytotoxicity test was recently proposed by Zawodniak and colleagues<sup>63</sup> using a combination method with flow cytometry and enzyme-linked

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