Drug reaction

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LOGICAL APPROACH TO DETERMINE THE CAUSE OF A DRUG ERUPTION

clinical characteristics

- Type of primary lesion (e.g. urticaria, erythematous papule, pustule, purpuric papule, vesicle or bulla)
- Distribution and number of lesions . Mucous membrane involvement, facial edema
- Associated signs and symptoms: fever, pruritus, lymph node enlargement, visceral involvement

Logical approach to determine the cause of A drug eruption

- **Chronological factors** .
- Document all drugs to which the patient has been exposed (including OTc and complementary) and the dates of administration .
- Date of eruption .
- Time interval between drug introduction (or reintroduction) and skin eruption . Response to removal of the suspected agent Response to rechallenge

- The time between initiation of the drug and the onset of the skin eruption is a key element in identifying the offending drug, as most immunologically mediated reactions occur within 8 to 21 days after initiation of a new medication.
- Evolution after drug withdrawal may be helpful, as the cutaneous eruption usually clears when the suspected drug IS discontinued.

- However; this assessment may prove difficult in the case of drugs with a long half-life or "persistent" drug reactions such as lichenoid and photoallergic eruptions or drug-induced pemphigus foliaceus and suhacute cutaneous LE.

- Of note, cutaneous patch tests with the offending agent are frequently positive (80%of patients) after recovery from AGEP but are positive in only a minority of cases of SjS or TEN.

Exanthematous Drug Eruptions

- Exanthematous or morbilliform eruptions are the most common adverse drug reactions affecting the skin. They are often referred to as **maculopapular drug eruptions**.
- The major underlying mechanism is probably **immunologic**, and they are often considered to be cell-mediated hypersensitivity reactions.
- viral infections may increase the incidence of drug reactions, e.g. **aminopenicillin**-induced exanthematous eruptions in patients with infectious mononucleosis ranges from 33% to 100%.

Contributing Factors

- **Underlying disorders**

❑ Viral infections, particularly Epstein-Barr virus, cytomegalovirus, and human herpesviruses 6 and 7 are associated with an increased risk of cutaneous drug eruptions .

❑ Patients with inborn, acquired, or iatrogenic immunodeficiency, HIV infection, cystic fibrosis, and, possibly, autoimmune disorders, also are prone to develop drug-induced exanthems .

- **Comedication**

- The concomitant administration of multiple medications may result in a more frequent occurrence of drug-induced exanthems. Hypersensitivity reactions have been reported in patients treated with high doses of valproate and lamotrigine, probably due to sensitization to one molecule or metabolite

- Overall, most drug classes can induce an exanthematous eruption in ~1% of treated patients.
- Higher risk medications (>3% of treated patients develop an eruption) include
- aminopenicillins,
- allopurinol,
- sulfonamides,
- cephalosporins,
- and aromatic anticonvulsants.

- The cutaneous eruption classically begins 7 to 14 days after the start of a new medication and can even occur a few days after the drug has been discontinued.

- However, the eruption may develop sooner, especially in cases of inadvertent re challenge.

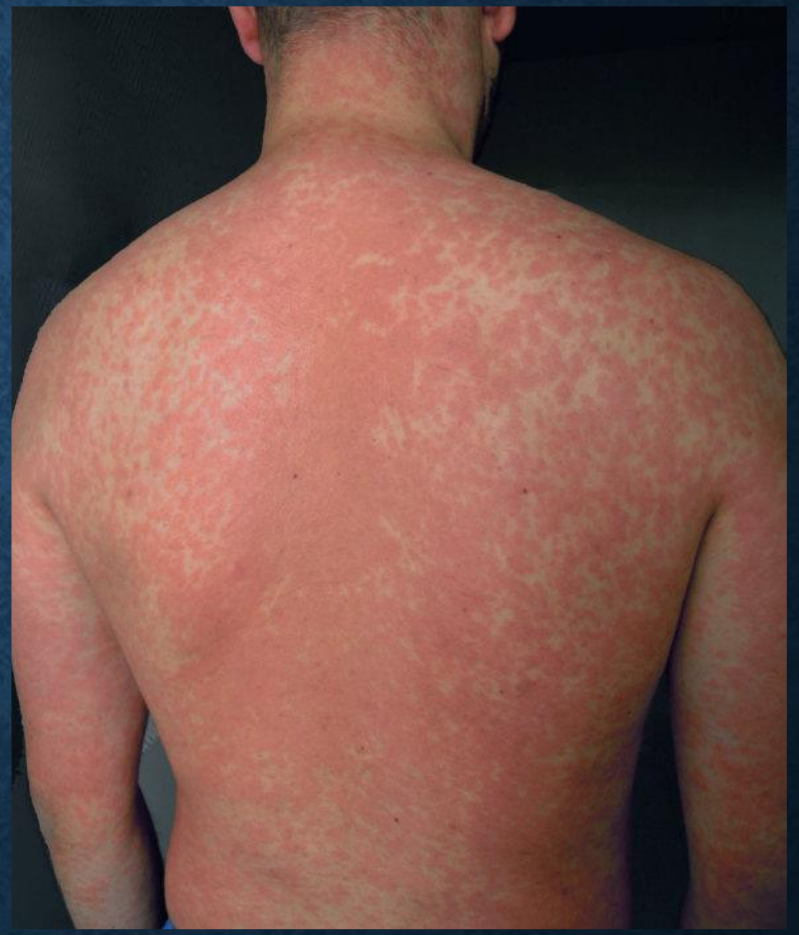
- The lesions begin as erythematous macules in a symmetric distribution that sometimes become slightly palpable.

- The eruption begins on the trunk and upper extremities and progressively becomes confluent .

- It is typically polymorphous with morbilliform or sometimes urticarial lesions on the limbs, confluent areas on the thorax ,and purpuric lesions on the ankles and feet.
- Red macules and papules become confluent in a symmetric, generalized distribution that often spares the face .
- Itching is common.
- Mucous membranes are usually spared.
- low-grade fever are often present.

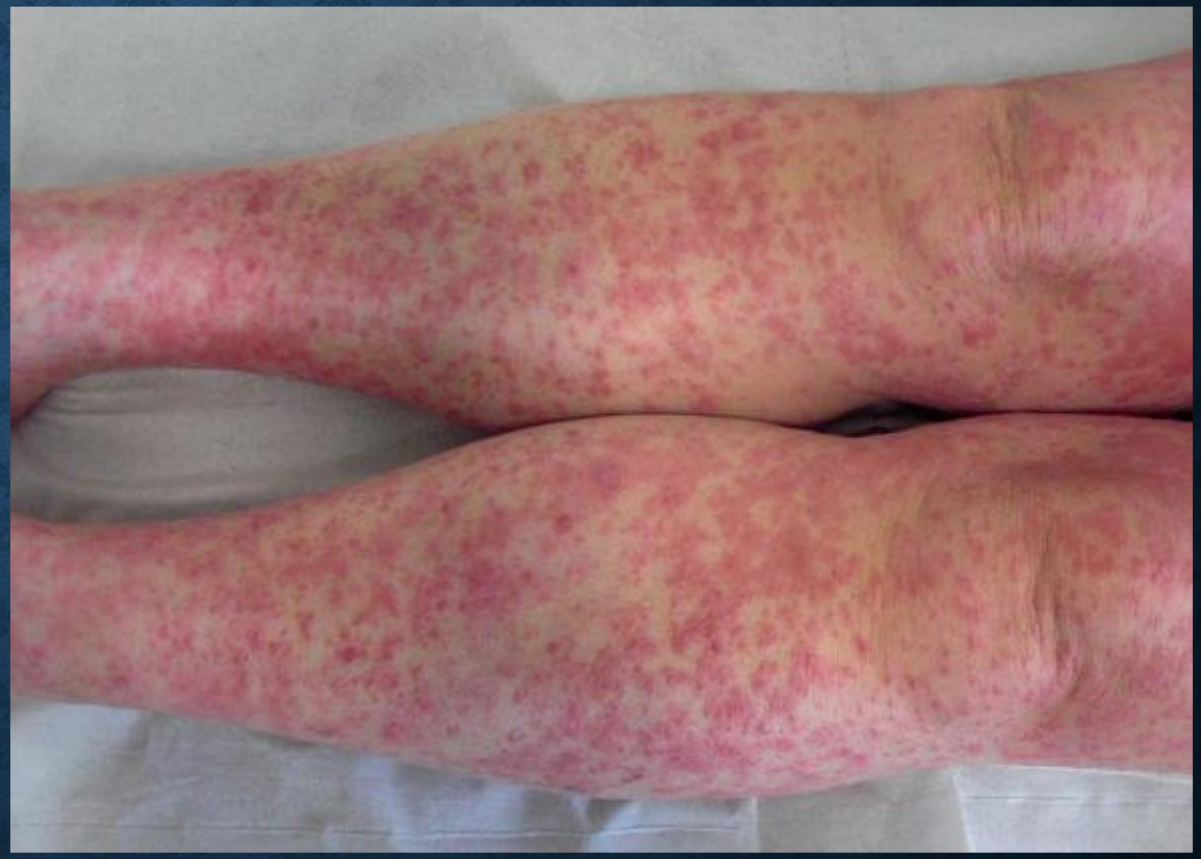
Morbilliform (exanthematous) drug eruptions

Erythematous papules and urticarial lesions with confluence on the mid back induced by amoxillin.



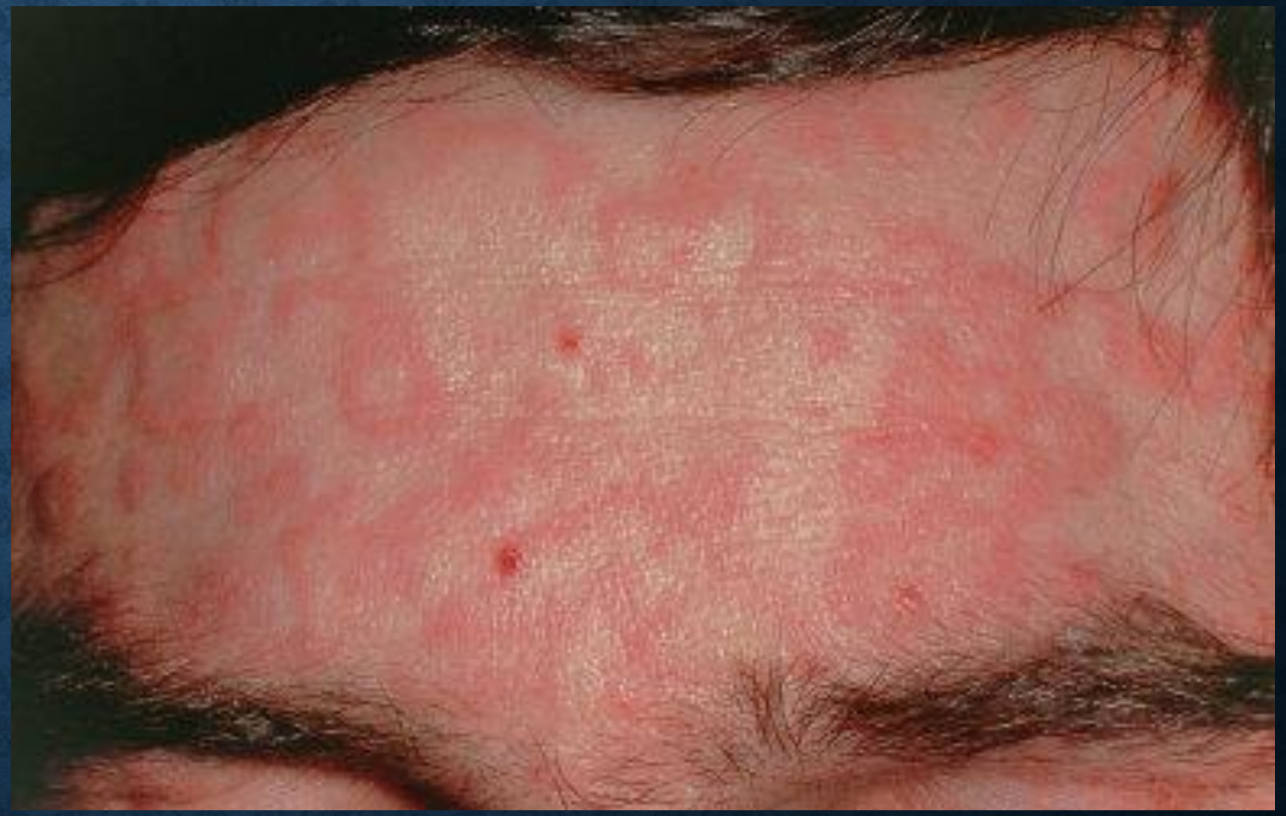
Morbilliform (exanthematous) drug eruptions

Due to dependency, lesions on the distal lower extremities can become petechial or purpuric



Morbilliform (exanthematous) drug eruptions

Pink papules and annular lesions on the forehead due to phenobarbital.



- Signs and symptoms that point to the possibility of a more severe drug-induced eruption include
- edema of the face,
- pustules,
- vesicles,
- dusky or painful lesions,
- skin fragility,
- mucous membrane involvement,
- elevation of acute-phase proteins,
- and marked peripheral blood eosinophilia.

CLINICAL COURSE

Most exanthematous drug eruptions are of mild to moderate severity and do not cause major morbidity. The eruption evolves rapidly, reaches the maximal extent approximately two days after the elimination of the causative drug, and resolves in 5 to 14 days . Occasionally, a mild eruption subsides despite continuation of the medication.

Resolution often occurs with some desquamation. In patients with darker skin tones, postinflammatory hyperpigmentatio

CHARACTERISTICS OF MAJOR DRUG-INDUCED ERUPTIONS				
Clinical presentation	Percentage that are drug-induced (%)	Time interval	Mortality (%)	Selected responsible drugs
Exanthematous eruption	Child: 10–20 Adult: 50–70	4–14 days	0	Aminopenicillins Sulfonamides Cephalosporins Anticonvulsants (aromatic) Allopurinol Abacavir Nevirapine

Treatment

- Treatment is largely supportive.
- Topical antipruritics and corticosteroids may help to alleviate pruritus.
- Discontinuing the offending agent is the first therapeutic intervention. “Treating through”, i.e. continuing the drug despite the cutaneous eruption, can be considered when the suspected drug is of paramount importance for the patient and there is no satisfactory substitute drug. Usually, the eruption will disappear, but a few patients may experience progressive worsening, leading to erythroderma.
- Desensitization may be considered in HIV-infected patients who require sulfonamides.

SUMMARY

- Exanthematous (morbilliform) drug eruptions are the most common type of adverse drug reaction, occurring in approximately 2 percent of individuals exposed to drugs.
- Exanthematous drug eruptions are characterized by erythematous macules and papules that predominantly involve the trunk and proximal extremities .Mucosal involvement is usually absent.
- In most patients, the rash develops within 5 to 14 days of treatment, but may occur within two or three days in previously sensitized patients, and resolves in 5 to 14 days after drug withdrawal .
- Systemic symptoms include pruritus, low-grade fever, and mild eosinophilia.
- We generally use high-potency topical corticosteroids one to two times per day for one week. Antihistamines (eg, diphenhydramine, hydroxyzine, cetirizine) are given orally until pruritus subsides.
- We suggest **not** routinely using systemic corticosteroids for the treatment of uncomplicated exanthematous drug eruptions .However, in patients with systemic or cutaneous symptoms suggesting a severe cutaneous reaction ,a short course of moderate/high-dose systemic corticosteroids may be beneficial.

Urticaria

- Urticaria is characterized by transient erythematous and edematous papules and plaques that are usually associated with pruritus.
- The primary effector cell is the cutaneous mast cell which releases histamine and other inflammatory media
- Central pallor can be seen as in the wheal-and-flare reaction to histamine. The lesions vary in size
- They can appear anywhere on the body, including the palms, soles or scalp.
- The duration of an individual lesion is usually a few hours to 24 hours; when the urticaria resolves, the skin is normal in appearance.
- Although drugs are thought to be responsible for < I0% of all cases of urticarial.

- The major drugs responsible for immunologically based urticaria are antibiotics, especially penicillins and cephalosporins, and, less often, sulfonamides and tetracyclines (in particular minocycline).

- In anaphylactoid reactions, vasodilation results from the liberation of large amounts of histamine, bradykinin, and/or leukotrienes.

- **Acetylsalicylic acid** is the classic example of a drug that induces an anaphylactoid reaction; the majority **of urticarial reactions to radiocontrast** media are non immunologic .

- Allergic reactions to **latex in gloves** or medical devices can induce local or generalized urticaria, especially in the case of direct contact with mucosal surfaces

- The most important step in the treatment of drug-induced urticaria is withdrawal of the causative agent.

- Treatment consists primarily of H1 antihistamines.

Angioedema

- Angioedema is a reflection of transient edema of the deep dermal, subcutaneous and submucosal tissues.
- It is associated with urticaria in 50% of cases and may be complicated by life-threatening anaphylaxis.
- Angioedema occurs in 1 to 2 per 1000 new users of angiotens inconverting enzyme (ACE) inhibitors, a rate that is probably higher than the risk associated with penicillin.

- The most severe cases of angioedema may start within a few minutes after drug administration.

Angioedema

- However, in the case of ACE inhibitor-induced angioedema, lesions may appear from I day to several years after starting the drug; most appear within the first year.

- The major drugs implicated in angioedema, besides penicillins and ACE inhibitors, are NSAIDs, radiographic contrast media and, more recently, monoclonal antibodies .

- Although angiotensin II receptor antagonists do not increase levels of bradykinin, they are also associated with angioedema, albeit less frequently.

Angioedema

- The most common clinical presentation is an acute, asymmetric, pale or pink, subcutaneous swelling involving the face.

- Involvement of the oropharynx, larynx, and epiglottis can lead to impaired swallowing and stridor.

- Occasionally, in drug-induced angioedema, there is edema of the intestinal wall with abdominal pain, nausea, vomiting, and diarrhea.

Anaphylaxis

- Anaphylaxis consists of an acute life-threatening reaction that can result from exposure to a number of drugs.

- It occurs in about 1 per 5000 exposures to **penicillin** and combines skin (urticaria and/or angioedema) with systemic manifestations such as hypotension and tachycardia.Occasionally, there is ***hypotension*** in the absence of cutaneous lesions.

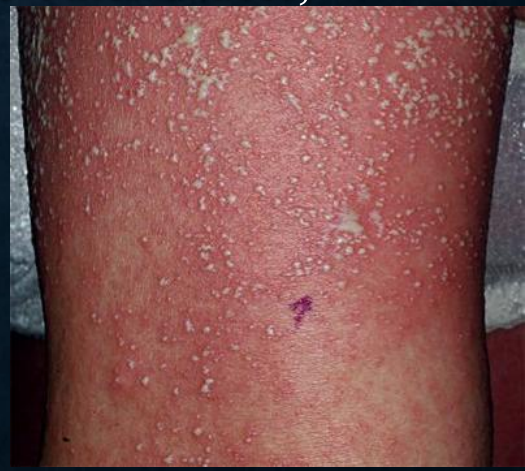
- In severe cases, the patient becomes unconscious as a result of cardiovascular shock and may die.
- Serious cases of anaphylactic shock tend to appear shortly (within minutes) after drug administration and are more commonly seen with parenteral administration as compared to oral ingestion.

- Patients who have been receiving b blockers may have a stunted response to the epinephrine.

Urticaria	<10	Minutes to hours	0	Penicillins Cephalosporins NSAIDs Monoclonal antibodies Radiocontrast media†
Anaphylaxis	30	Minutes to hours	5	

Acute generalized exanthematous pustulosis (AGEP)

- It is an acute febrile drug eruption characterized by numerous small, primarily non-follicular, sterile pustules, arising within large areas of edematous erythema. ever and peripheral blood leukocytosis are usually present.
- The incidence of AGEP has been underestimated and many cases have been confused with pustular psoriasis.
- More than 90% of cases of AGEP are drug-induced. Occasionally, it may be due to other causes, e.g. an enteroviral infection or exposure to mercury.



EPIDEMIOLOGY

- the incidence of AGEP is one to five per million per year .
- AGEP can occur at any age, although it most often affects adults. the mean age was 56 years .
- Both sexes are affected, with a slight female predominance

ETIOLOGY AND PATHOGENESIS

- **Eliciting factors** :
- AGEP is caused by **drugs** in approximately 90 percent of cases . **Anti-infective agents , antimalarials, and the calcium channel blocker diltiazem** are the most frequently reported triggers of AGEP.

- There are isolated reports of AGEP associated with **viral, bacterial, or parasitic** infections (eg, parvovirus B19, cytomegalovirus, coxsackie B4, *Mycoplasma pneumoniae)*; spider bites; and herbal medications .

- However, in some cases the cause remains undetermined.

ETIOLOGY AND PATHOGENESIS

- **Immunologic mechanisms** :
- The pathomechanism of AGEP has been only partially investigated. AGEP is a T cell mediated neutrophilic inflammation involving drug-specific $CD4^+$ T cells, cytotoxic $CD8^+$ T cells, and inflammatory cytokines and chemokines

- **Genetics**
- Recessively inherited mutations in the *IL36RN* gene encoding the interleukin-36 receptor antagonist (IL-36Ra) have been found in generalized pustular psoriasis .
- This finding suggests that generalized pustular psoriasis and AGEP may share a common pathogenetic pathway, making it difficult in some cases to distinguish between the two entities.

- the short interval explain (4 days) between drug administration and the onset of the eruption, as this suggests an immunologic recall phenomenon.

- In a series of 97 cases of AGEP, the median time between drug exposure and development of symptoms was one day for antibiotics and 11 days for all other drugs.

- The percentage of positive patch tests to the incriminated drugs is high (**up to 80**%).
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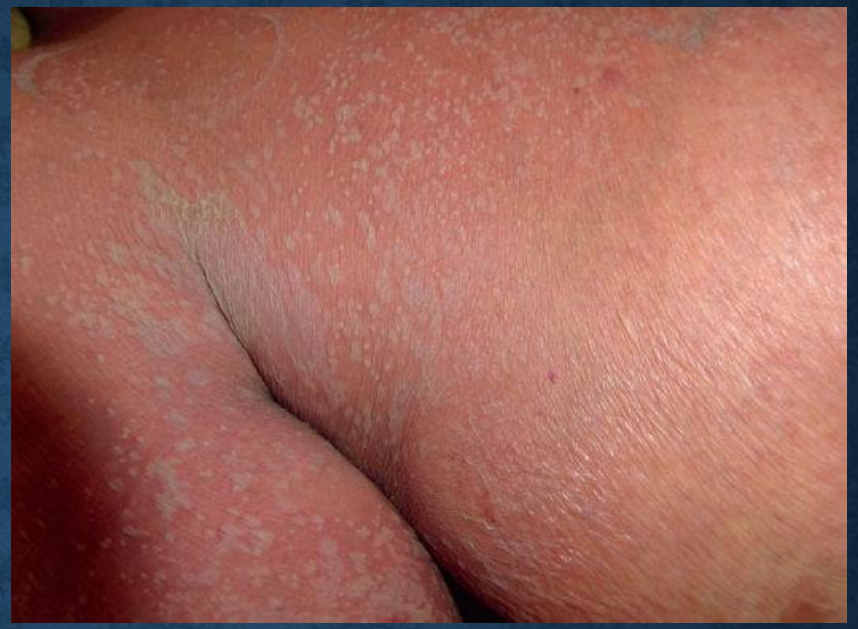
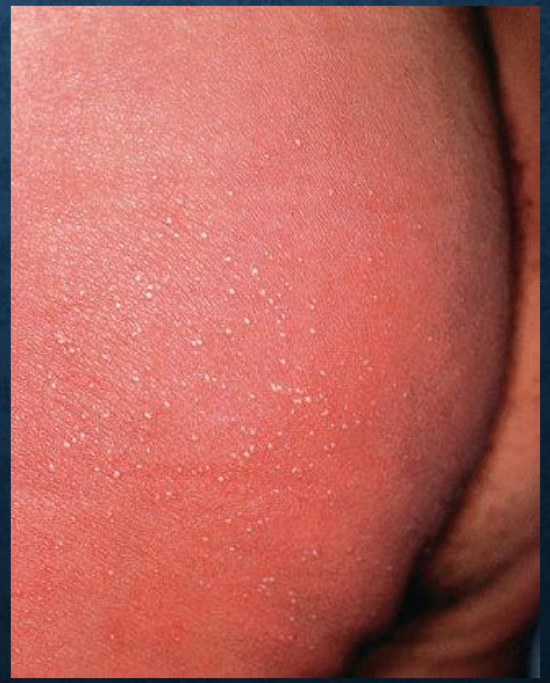
- Clinically, AGEP is characterized by a high fever, with lesions beginning on the face or in the major intertriginous zones (i.e. axillae and groin) and then disseminating over a few hours.

numerous sterile pustules with superficial epidermal detachment in areas where the pustules have become confluent in a patient receiving amoxicillin.



Diffuse erythema of the buttock with multiple small sterile pustules due to a cephalosporin.



- Numerous small <5 mm non-follicular, sterile pustules arise within large areas of edematous erythema.

- There may be associated burning or pruritus or both.

- Edema of the face and hands, purpura, vesicles, bullae, erythema multiforme-like lesions and mucous membrane involvement are additional findings observed in approximately 50% of patients.

- Involvement of mucous membranes is unusual and, when present, is limited to erosions of the lips.

- During the acute phase, fever above 38°C (100.4°F), leukocytosis with a neutrophil count >7000/microL, and mild eosinophilia are often present.

- Organ involvement is not common in AGEP, but can occur, particularly in older or compromised patients. A mild increase in serum transaminases or a reversible reduction in the creatinine clearance have been reported in some patients

- The lesions last 1 to 2 weeks and are followed by a superficial desquamation.

- Antibiotics are the primary drugs implicated in AGEP. Beta-lactam antibiotics (e.g. penicillins, aminopenicillins, cephalosporins) and macrolides are the most frequently responsible medication, followed by calcium channel blockers (in particular diltiazem) and antimalarials.

- Additional cases have been associated with carbamazepine, acetaminophen and a wide range of antimicrobials (e,g. terbinafine, metronidazole, isoniazid, vancomycin, doxycycline).

Acute generalized exanthematous pustulosis (AGEP)	70–90	< 4 days	1–2	β-Lactam antibiotics Macrolides Calcium channel blockers

MANAGEMENT

- **Drug withdrawal and supportive measures**
- Older or compromised patients with fever and widespread eruption may require fluid, electrolyte, and nutritional support.
- **Symptomatic treatment** — For symptomatic relief of pruritus and skin inflammation, we suggest topical rather than systemic corticosteroids.
- We use medium potency corticosteroids .They are applied twice a day for one week. In the desquamation phase, emollients may be helpful in restoring the skin barrier function.

SUMMARY

- numerous nonfollicular, sterile, small pustules on a background of edematous erythema . In approximately 90 percent of cases, AGEP is caused by drugs, most often **antibiotics, calcium channel blockers and antimalarials**
- Fever above 38°C (100.4°F) and leukocytosis with a neutrophil count >7000/microL are usually present.
- The eruption resolves spontaneously in one to two weeks after the discontinuation of the offending drug.
- The rapid resolution of the eruption after drug discontinuation also supports the diagnosis.
- For symptomatic relief of pruritus and skin inflammation, we suggest topical corticosteroids .
- We generally use medium potency topical corticosteroids . They are applied twice a day for one week.

Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)

- It is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement (liver, kidney, lung) .
- DRESS may occur in children , but most cases occur in adults without sex predilection
- Clinically, this hypersensitivity syndrome develops 2 to 6 weeks after drug initiation, later than most other immunologically mediated skin reactions. With re-exposure, there can be a shorter time to onset.
- Fever and a cutaneous eruption are the most common symptoms, seen in 85% and 75% of patients, respectively.
- Cutaneous involvement usually begins as a morbilliform eruption, which later becomes edematous, often with a follicular accentuation.

Etiology AND RISK FACTORS

- Drug causality is determined in approximately **80 percent** of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) .
- The incidence of DRESS has been estimated to be between I in 1000 and 1 in 10000 exposures to drugs such as anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital) and sulfonamides.
- The frequency varies depending upon the type of drug and immune status of the patient.
- It ranges from 1 to 5 per 10,000 patients exposed to the anticonvulsants, carbamazepine and phenytoin, and appears to be higher among patients taking lamotrigine(1 per 300 adults and 1 per 100 children exposed)

DRUGS ASSOCIATED WITH DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS SYNDROME (DRESS)	
Drug category	**Specific drugs**
Anticonvulsants	**Carbamazepine, lamotrigine*, phenobarbital, phenytoin**, oxcarbazepine, zonisamide > valproic acid
Antimicrobials	Ampicillin, cefotaxime, **dapsone**, ethambutol, isoniazid, linezolid, metronidazole, **minocycline**, pyrazinamide, quinine, rifampin, sulfasalazine (salazosulfapyridine), streptomycin, **trimethoprim–sulfamethoxazole**, teicoplanin, **vancomycin**
Antiretrovirals	**Abacavir**, **nevirapine**, zalcitabine
Antidepressants	Bupropion, fluoxetine
Antihypertensives	Amlodipine, captopril
NSAIDs	Celecoxib, ibuprofen
Miscellaneous	**Allopurinol****, azathioprine, imatinib, mexiletine, ranitidine, ziprasidone
*Especially when coadministered with valproic acid. **Full doses in the setting of renal dysfunction a risk factor.	

Table 21.12 Drugs associated with drug reaction with eosinophilia and systemic symptoms syndrome (DRESS). Most commonly associated drugs are in **bold**. NSAIDs, nonsteroidal anti-inflammatory drugs.

- Antiepileptic agents (eg, carbamazepine, lamotrigine, phenytoin, phenobarbital) and allopurinol are the most frequently reported causes .
- DRESS with renal involvement has been reported in patients treated with febuxostat, a newly developed xanthine oxidase inhibitor with a chemical structure different from allopurinol and approved for the treatment of hyperuricemia .
- Febuxostat-induced DRESS occurred in one patient with a history of allopurinol-induced DRESS, suggesting a possible cross-reaction between the two drugs.

PATHOGENESIS

- **Drug-specific immune response**

- **Virus reactivation** :Also implicated in the pathogenesis of DRESS is reactivation of human herpes viruses, primarily HHV-6 and HHV-7, but also CMV and EBV.

- Thus, DRESS is primarily a strong, drug-specific immune reaction that acts as a trigger of viral reactivation.

CLINICAL PRESENTATION

- In most patients, the reaction begins two to six weeks after the initiation of the offending medication .
- The latency between drug exposure and onset of symptoms is considerably longer in DRESS than in most drug eruptions (typically, 4 to 9 days for morbilliform eruptions and 4 to 28 days for SJS/TEN)
- Fever (38 to 40°C), malaise, lymphadenopathy, and skin eruption are the most common initial symptoms

- Additional manifestations include vesicles, tense bullae induced by dermal edema, follicular as well as non-follicular pustules (~20% of patients), erythroderma and purpuric lesions.
- The face, upper trunk and extremities are usually the initial sites of involvement.
- **Edema of the face** is a frequent finding and is a hallmark of DRESS.
- Inflammation and pain of mucous membranes is present in nearly one-half of patients.
- The extent of the BSA involvement is an important marker of disease severity
- Lymph nodes are often enlarged, and sometimes arthralgias or even arthritis may be seen.

Laboratory abnormalities

- Leukocytosis with eosinophil counts >700/microL (in 50 to 90 percent of cases)
- Atypical lymphocytosis with large activated lymphocytes, lymphoblasts, or mononucleosis-like cells (in 30 to 70 percent of cases)
- Increased serum alanine aminotransferase (in up to 80 percent of cases)
- Reactivation of human herpesvirus-6 (HHV-6) and other viruses (in 40 to 60 percent of tested patients)

Organ involvement

- Involvement of at least one internal organ occurs in approximately 90 percent of patients; in 50 to 60 percent of patients, two or more organs are involved, most frequently **liver (**60 to over 80 percent of cases), **kidneys** (10 to 30 percent of cases), **and lungs** (5 to 25 percent of cases).
- **Liver** :
- Hepatomegaly and jaundice may be present, but most often hepatitis is **asymptomatic a**nd detected by routine liver function tests (LFT)..
- Liver injury was cholestatic-type in 37 percent of cases, mixed type in 27 percent, and hepatocellular-type in 19 percent.

Organ involvement

- liver involvement is defined by the finding of a serum level of ALT **greater than twice the** upper limit of normal values and/or alkaline phosphatase greater than 1.5 times the upper limit of normal values on at least two different dates.
- LFT abnormalities are generally mild and transient, but severe impairment of liver function may occur
- Severe hepatitis is responsible for the majority of deaths associated with DRESS. Markedly elevated aspartate aminotransferase and bilirubin with jaundice and presence of hepatic encephalopathy are the most important predictors of death or liver transplantation .

- **Kidney** :

- Renal involvement, manifesting as acute interstitial nephritis, occurs in 10 to 30 percent of DRESS cases, most often in those induced by allopurinol . Older age and preexisting alterations of renal function may be predisposing factors.

- Renal abnormalities include a moderate increase in creatinine level, low grade proteinuria, and abnormal urinary sediment with occasional eosinophils.

- **Lung** :
- Pulmonary involvement presents with nonspecific symptoms, including cough, fever, and tachypnea/dyspnea
- pulse oximetry may reveal an unsuspected hypoxemia.
- Chest radiograph or CT scan may provide evidence of interstitial pneumonitis and/or pleural effusion.

- **Other organs** :
- Heart (eosinophilic myocarditis, pericarditis)
- Gastrointestinal tract (diarrhea, mucosal erosions, bleeding)
- Pancreas (pancreatitis)
- Thyroid (autoimmune thyroiditis, appearing often late, as a sequel of DRESS)
- Brain (encephalitis, meningitis)
- Muscle (myositis, increase in creatine kinase)
- Peripheral nerves (polyneuritis)
- Eye (uveitis)

CLINICAL COURSE

- The skin eruption and visceral involvement generally resolve gradually after drug withdrawal.
- The average time to recovery is **six to nine weeks** .
- In up to 20 percent of cases, the disease may persist for several months with a succession of remissions and relapses.
- Factors associated with a prolonged course include a more severe liver involvement and presence of mononucleosis-like atypical lymphocytosis .
- Relapses have been reported concurrently with human herpesvirus 6 reactivation .
- It seems anyhow prudent to avoid treatment with beta-lactam antibiotics during the course of DRESS.
- Prominent eosinophilia is common and is a very characteristic feature. It is often accompanied by mononucleosis-like atypical lymphocytosis.

Diagnosis

- In typical cases, the diagnosis is based upon the following findings :
- History of exposure to a high-risk medication, such as allopurinol or antiepileptic drugs in the two to six weeks before the onset of symptoms.
- Morbilliform eruption progressing to confluent and infiltrated erythema **or** exfoliative dermatitis involving ≥90 percent of the total body surface area (BSA)
- Hematologic abnormalities (eosinophilia >700/microL and/or atypical lymphocytosis).
- Systemic symptoms and organ involvement which may include:
- Fever (38 to 40°C [100.4 to 104°F])
- Enlarged lymph nodes
- Abnormal liver function tests
- Renal impairment
- Interstitial pneumonia and/or pleural effusion
- Myocarditis

- The cutaneous and visceral involvement may persist for several weeks or months after drug withdrawal, and additional sites of involvement (e.g. cardiac, thyroid) may develop weeks or months later, including following a taper of corticosteroids.

- Overall mortality due to DRESS ranges from 2 to 10% .

- Elevation of hepatic enzymes can be a worrisome finding and requires serial evaluation.
- Thyroid and cardiac dysfunction (as detected by an ECG and echocardiogram) may develop as delayed complications and patients should therefore undergo longitudinal evaluation

MANAGEMENT

- **Drug withdrawal and supportive measures** .
- **Patients without severe organ involvement**
- Patients with DRESS without clinical, laboratory, or imaging evidence of renal or pulmonary involvement and those with only modest elevation of liver transaminases (ie, <3 times the upper limit of normal) can be treated symptomatically.
- For symptomatic relief of pruritus and skin inflammation, we suggest high or super high potency topical corticosteroids (rather than systemic corticosteroids. Topical corticosteroids are applied two to three times per day for one week.

Patients with severe organ involvement

- **Liver involvement** — The main treatment of drug-induced acute hepatitis is withdrawal of the offending drug. Systemic **corticosteroids** are of unproven benefit for most forms of drug hepatotoxicity and there is no consensus on their use. Patients should be followed by serial biochemical measurements. Hepatology consultation may be warranted in some cases.

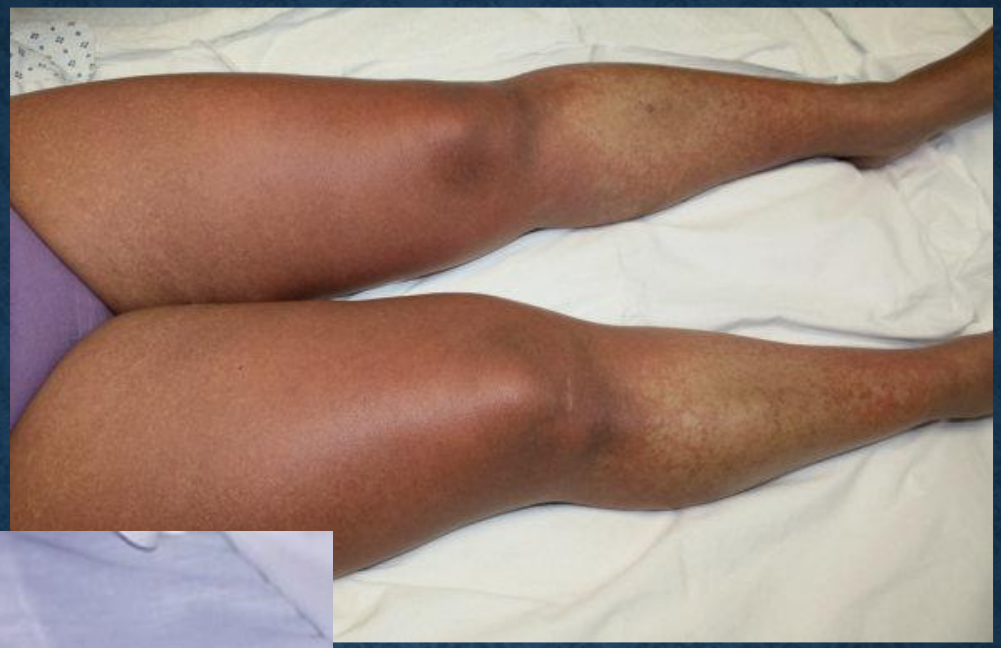
- **Lung or kidney involvement** — We suggest systemic corticosteroids for patients with severe involvement of the lungs (dyspnea, abnormal chest radiograph, hypoxemia) or kidneys (creatinine >150 percent basal level and proteinuria or hematuria).

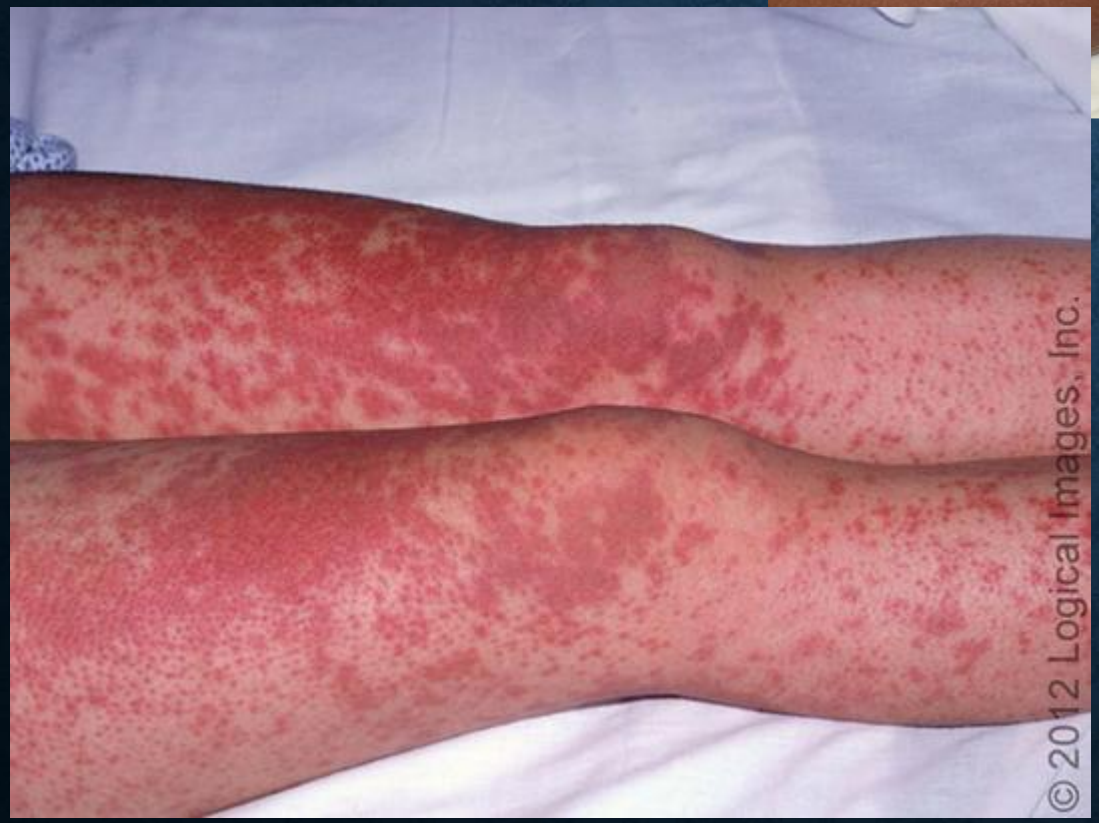
- We use a moderate to high dose of systemic corticosteroids (eg, 0.5 to 2 mg/kg per day of prednisone or prednisone equivalent). Systemic corticosteroids are given until clinical improvement and normalization of laboratory parameters are obtained and then tapered over the ensuing 8 to 12 weeks. A more rapid tapering may increase the risk of relapse.

- **cyclosporine** — There are a few reports of rapid resolution of DRESS with organ involvement with a short course of oral cyclosporine .
- Although evidence is limited, cyclosporine may be a second-line therapy for patients with DRESS and severe organ involvement who do not respond to systemic corticosteroids and for patients in whom corticosteroids are contraindicated

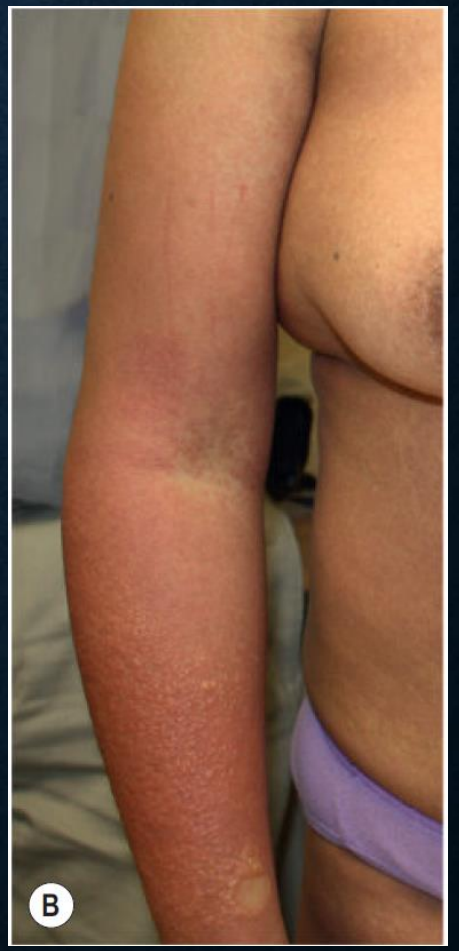
- Relapse can occur when the dosage is tapered, and, as a result, steroid therapy sometimes has to be maintained for several weeks and even months.
- Retrospective studies have reported a mortality rate for DRESS of 5 to 10 percent

Drug reaction with eosinophilia and systemic symptoms (DRESS) due to carbamazepine. **A** exanthematous eruption with confluence on the thighs





B edema and vesiculation on the forearm



ASSESSMENT AND LONGITUDINAL EVALUATION OF PATIENTS WITH DRESS (DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS)
Basic laboratory screening during the acute phase with recommended repetitive tests *in italics*^
• *CBC with differential, platelet count,* peripheral smear for atypical lymphocytes • *BUN, creatinine, urinalysis,* spot urine for protein:creatinine ratio* • *LFTs, creatine kinase (CK),* lipase, CRP • *TSH, free T4* (repeat at 3 months, 1 year, and 2 years) • Fasting glucose (in anticipation of systemic corticosteroids)
Additional testing
• ECG, troponin T, baseline echocardiogram • Quantitative PCR for HHV-6, HHV-7, EBV, CMV • Wright stain of urine for eosinophilia (prior to instituting corticosteroids) • ANA, blood cultures (exclusion criteria in RegiSCAR scoring system) • If hemophagocytic lymphohistiocytosis suspected (see Ch. 91)**, ferritin, triglycerides, LDH, BM examination
Further testing based upon laboratory abnormalities or signs and symptoms**
• Liver – PT, PTT, albumin • Renal – albumin, renal ultrasound (if laboratory abnormalities) • Cardiac – ECG, troponin T, echocardiogram • Neurologic – brain MRI • Pulmonary – CXR, PFTs • Gastrointestinal – endoscopy
^Testing is more frequent during the acute phase (e.g. twice weekly) with frequency also a reflection of disease severity. Longitudinal evaluation is recommended for at least one year. *Allows for immediate assessment for proteinuria. **Including during longitudinal evaluation.

Table 21.11 Assessment and longitudinal evaluation of patients with DRESS (drug reaction with eosinophilia and systemic symptoms). BM, bone marrow; BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; CRP, C-reactive protein; LDH, lactic dehydrogenase; LFTs, liver function tests; PFT, pulmonary function test; PT, prothrombin time; PTT, partial thromboplastin time; TSH, thyroid stimulating hormone.

Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS)	70–90	15–40 days	5–10	Anticonvulsants (aromatic) Lamotrigine (especially in combination with valproate) Sulfonamides Abacavir Allopurinol Dapsone Minocycline Nevirapine

summary

- Antiepileptic agents and allopurinol are the most frequently reported causes. Sulfonamides (eg, sulfasalazine), dapsone, minocycline, and vancomycin may also induce DRESS .
- There is evidence for a genetic predisposition to DRESS when related to allopurinol, carbamazepine, or dapsone.
- In most patients, the reaction begins two to six weeks after the initiation of the offending medication. Fever (38 to 40°C , malaise, lymphadenopathy, and skin eruption are the most common initial symptoms, but they are not invariably present.
- The morbilliform eruption can become confluent and progress to exfoliative dermatitis in some patients
- Hematologic abnormalities include leukocytosis with eosinophilia >700/microL and/or atypical lymphocytosis.
- Liver involvement occurs in 60 to 80 percent of patients.
- Kidney (tubulointerstitial nephritis), lung (interstitial pneumonitis), and other organs can also be involved.
- Patients with DRESS without clinical, laboratory, or imaging evidence of renal or pulmonary involvement and those with only modest elevation of liver transaminases (ie, <3 times the upper limit of normal) can be treated symptomatically.
- For symptomatic relief of pruritus and skin inflammation, we suggest high or super high potency topical corticosteroids
- For patients with acute drug-induced liver injury, the main treatment is withdrawal of the offending drug. Serial biochemical measurements should be performed to monitor liver function.
- For patients with severe interstitial nephritis or interstitial pneumonia, we suggest systemic corticosteroids . Prednisone 0.5 to 2 mg/kg per day is given until clinical improvement and normalization of laboratory parameters are obtained and then tapered over the ensuing 8 to 12 weeks.

Fixed drug eruption

- In fixed drug eruptions (FDE), the lesions develop I to 2 weeks after a first exposure. With subsequent exposures, they appear within 24 hours.
- Clinically, one or a few, round, sharply demarcated erythematous and edematous plaques are seen ,sometimes with a dusky, violaceous hue, central blister or detached epidermis .
- Cutaneous skin reactions occur in approximately 2 to 3 percent of patients taking drugs.
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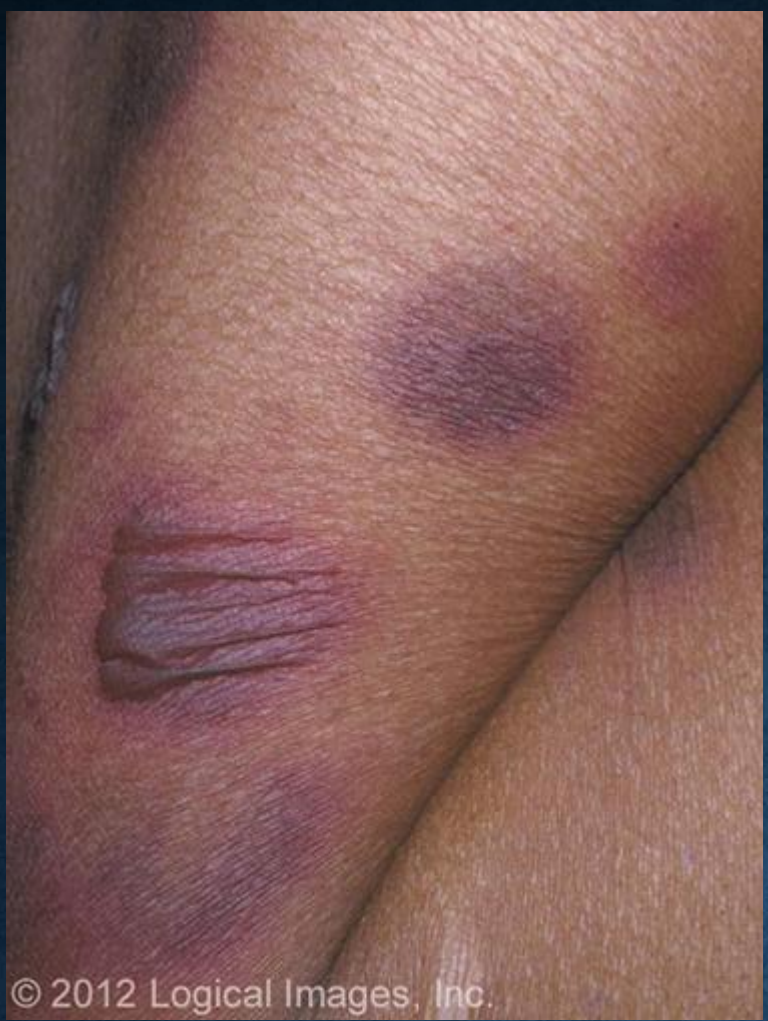
Fixed drug eruption

- FDEs occur in both sexes and in all age groups; in children, FDEs account for 14 to 22 percent of cutaneous drug reactions
- Rare severe atypical variants of FDE, including multiple, nonpigmenting, and generalized bullous variants.
- FDE may occur anywhere on the body. Sites of predilection include the lips, genitalia, perianal area, hands, and feet .
- An erosion may develop centrally and the lesions progressively fade over several days, often leaving a residual post inflammatory brown pigmentation .

- Systemic symptoms, such as fever and malaise, are usually absent.
- Pruritus and a burning or stinging sensation are common.
- On mucosal areas, erosions and ulcers may develop .
- FDE occasionally develops at the site of an antecedent trauma (eg, insect bite, burn, venipuncture) .
- After discontinuation of the offending drug, lesions resolve spontaneously in 7 to 10 days, leaving a persistent gray/brown or slate gray postinflammatory hyperpigmentation .
- Upon reexposure to the offending drug, lesions typically recur in the same site, but new lesions may develop elsewhere .
- After one or more localized eruptions, FDE rarely may evolve into a bullous generalized form mimicking Stevens-Johnson syndrome/toxic epidermal necrolysis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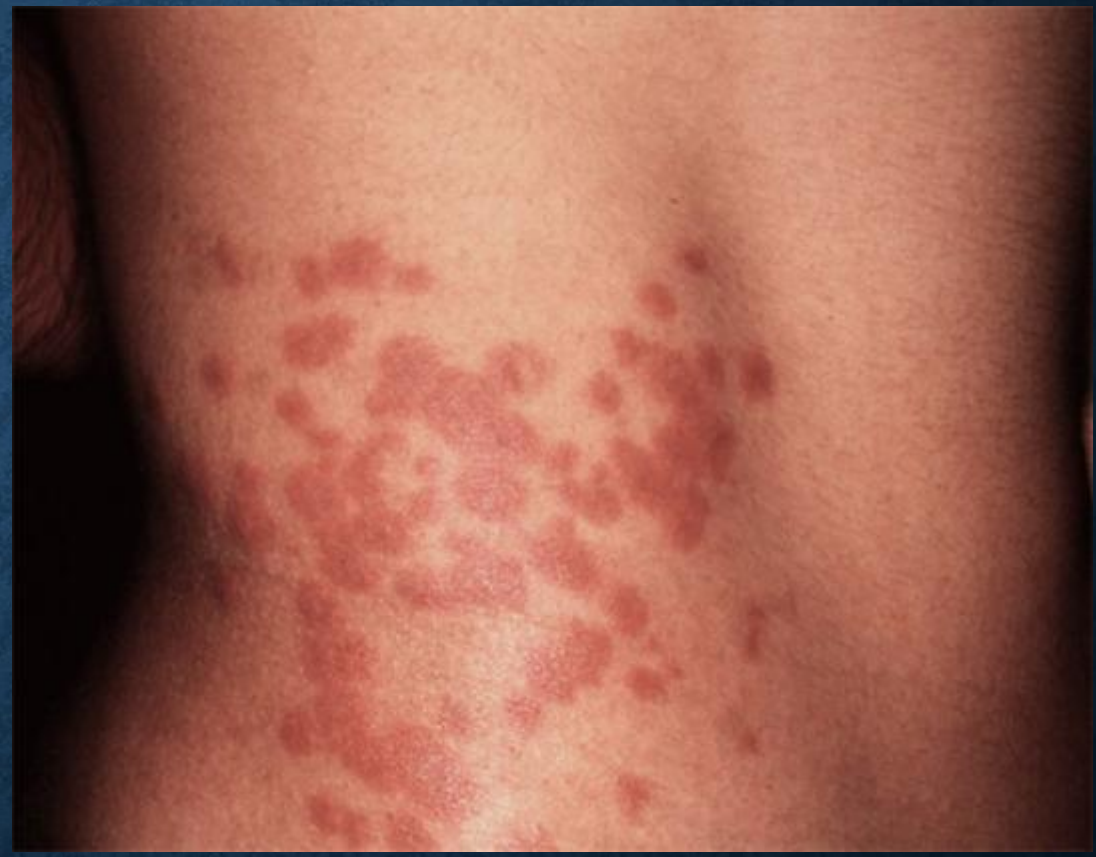
clinical variants

- **Erythema multiforme-like** FDE — FDE may present with targetoid lesions that mimic erythema multiforme . In contrast to erythema multiforme, these lesions have only two concentric zones of color with a darker, dusky hue in the center.
- **Generalized FDE** — The typical lesions are multiple and disseminated and involve the trunk and extremities, sparing the mucosal area.
- **Generalized bullous FDE** — Generalized bullous FDE (GBFDE) is an extremely rare form of FDE characterized by widespread red or brown macules or plaques with overlying large flaccid bullae . Systemic symptoms, such as fever, malaise, or arthralgias may be present.
- Patients with GBFDE can be misdiagnosed as having SJS/TEN, but in GBFDE mucosal involvement is usually absent or mild and the clinical course is favorable with rapid resolution in 7 to 14 days after drug discontinuation .
- However, the prognosis of GBFDE may be unfavorable in older patients, particularly in those with comorbidities.
- **Nonpigmenting FDE** — Nonpigmenting FDEs (NPFDEs) have been described .most often in association with the administration of pseudoephedrine. NPFDE presents with large solitary or multiple, well-circumscribed erythematous plaques that resolve without postinflammatory hyperpigmentation

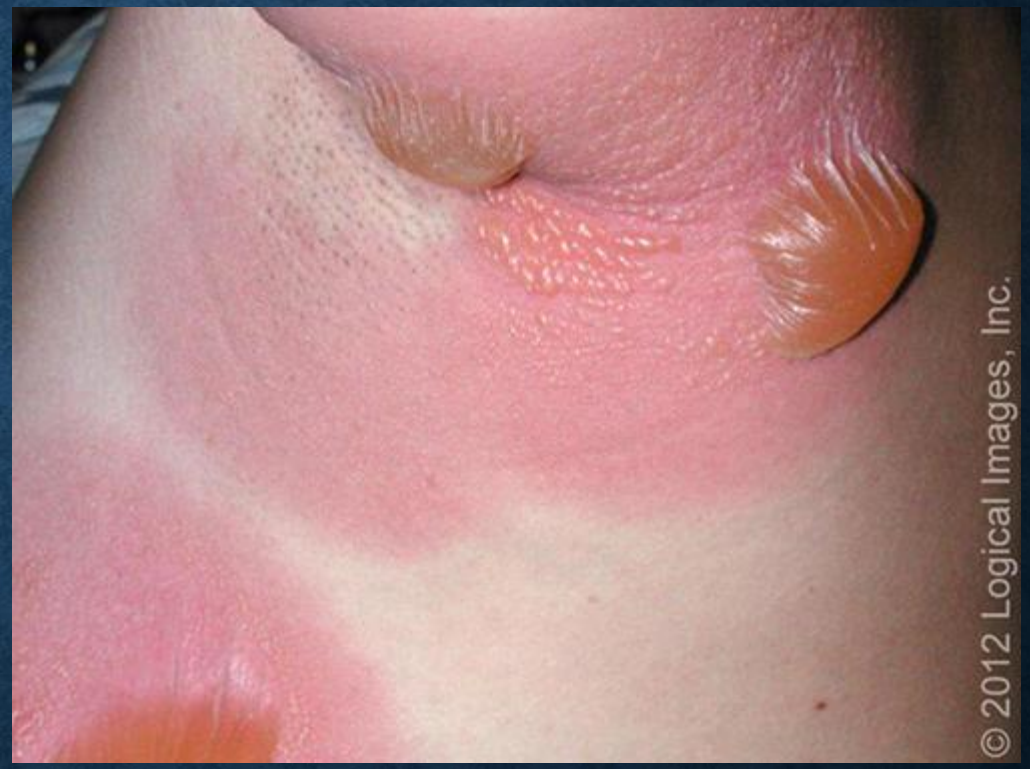
FIXED DRUG ERUPTION RESEMBLING ERYTHEMA MULTIFORME



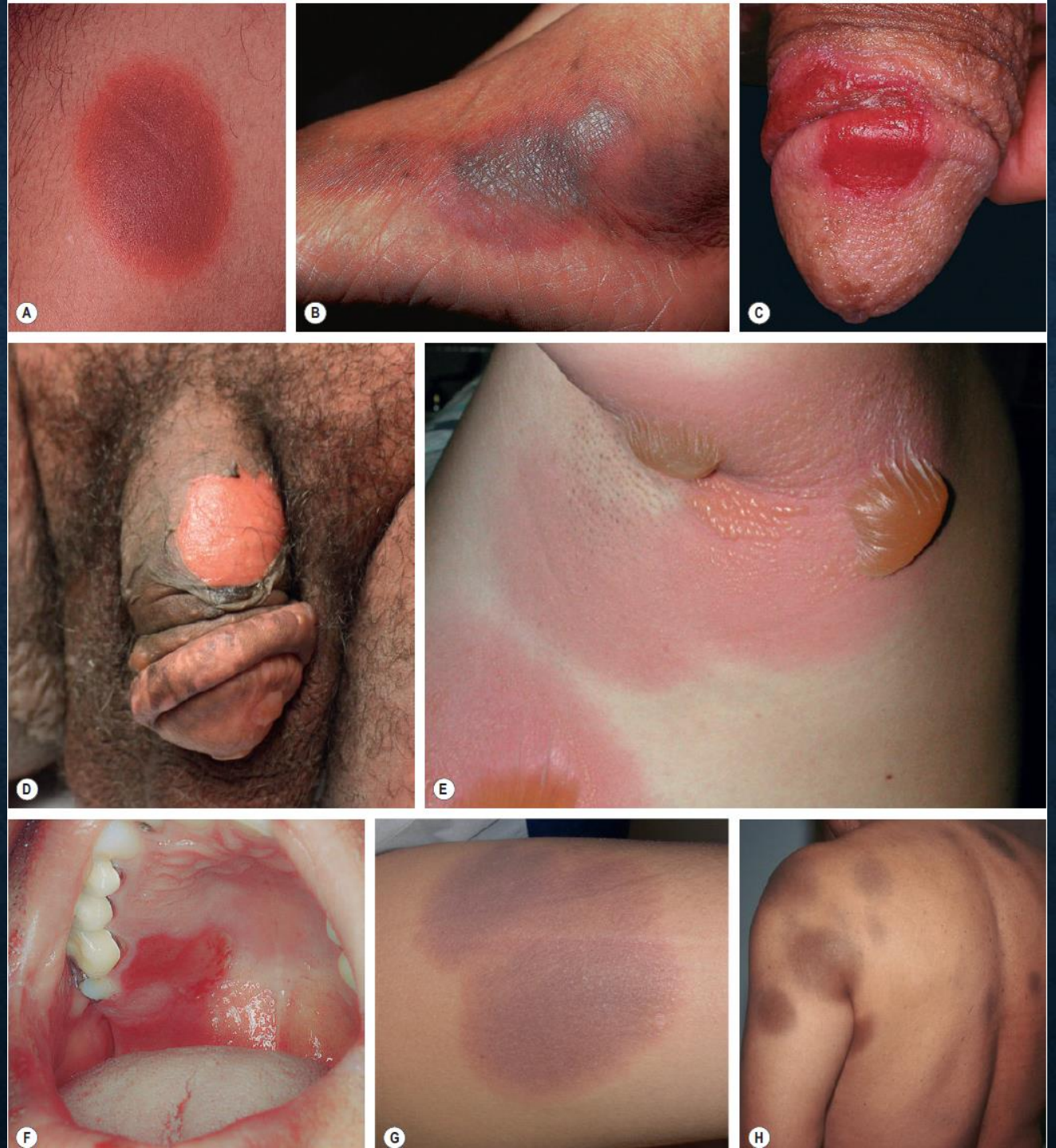
MULTIPLE (GENERALIZED)

FIXED DRUG ERUPTION

GENERALIZED BULLOUS FIXED DRUG ERUPTION



- Drugs most frequently associated with FDE include :
- Antibacterial agents (trimethoprim-sulfamethoxazole, tetracyclines, penicillins, quinolones, dapsone)
- Nonsteroidal anti-inflammatory drugs (NSAIDs; acetylsalicylic acid, ibuprofen, naproxen, mefenamic acid)
- Acetaminophen (paracetamol)
- Barbiturates
- Antimalarials
- proton pump inhibitors, and azole antifungal drugs
- A non-pigmenting variant of FDE, with large erythematous edematous plaques has also been described, occurring primarily after administration of pseudoephedrine. It has been also observed with other drugs, e.g. NSAIDs, acetaminophen, tetrahydrozoline (eyedrops).


A
B
C
D
E
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H

Fixed drug eruption	100	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	0	TMP-SMX NSAIDs Tetracyclines Pseudoephedrine*

Management

- **Drug withdrawal and avoidance** : After drug discontinuation, lesions resolve without treatment in a few days leaving PIH.
- **Symptomatic treatment** — The treatment of FDE is largely symptomatic and aimed at the relief of pruritus.
- For patients with single or a small number of lesions, we suggest medium to high potency topical corticosteroids and systemic antihistamines. Topical corticosteroids are applied two times per day for 7 to 10 days. Oral H1 antihistamines are generally used, including:
- diphenhydramine – 25 to 50 mg orally every four to six hours for adults and children ≥12 years; 12.5 to 25 mg orally every four to six hours for children 6 to 11 years; and 6.25 mg orally every four to six hours for children 2 to 5 years. Diphenhydramine is continued until pruritus subsides.
- Hydroxyzine – 25 mg orally three to four times per day for adults and children ≥6 years; 2 mg/kg per day orally divided every six to eight hours for children <6 years. Hydroxyzine is continued until pruritus subsides.
- For patients with generalized FDE or generalized bullous FDE, particularly if systemic symptoms are present, a short course of moderate dose systemic corticosteroids (eg, prednisone 0.5 to 1 mg/kg per day for three to five days) may be beneficial.

SUMMARY

- Fixed drug eruption (FDE) is a cutaneous drug reaction that characteristically recurs in the same locations upon reexposure to the offending drug.
- Antibacterial sulfonamides, antibiotics, nonsteroidal antiinflammatory drugs, analgesics, and hypnotics are the most frequent causes of FDE.
- FDE typically presents with solitary round to oval, dusky red to brown/black macules that may evolve into edematous plaques or bullae .
- Sites of predilection include the lips, genitalia, perianal area, and extremities
- In rare cases, FDE may present with atypical features, including generalized bullous FDE and nonpigmenting FDE that mimic more severe drug eruptions such as Stevens-Johnson syndrome/toxic epidermal necrolysis
- Discontinuation and avoidance of the offending drug is the most important aspect of management of FDE.
- Symptomatic treatment of the acute eruption may include medium to high potency topical corticosteroids .

Thank you for your attention

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