DRUG ALLERGY. STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS. ALLERGY TO ANESTHETIC AGENTS. CONTRAST MEDIUM REACTIONS.

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Definition

Drug allergy is a type of unpredictable reaction-related to individual's immunological response and, on occasion, to genetic differences in susceptible patients

Drug allergy refers to immunologically mediated drug hypersensitivity reactions

These may be either immunoglobulin E (IgE)–mediated (immediate) or non–IgE-mediated (delayed) hypersensitivity reactions with T cells

Definition of drug hypersensitivity reactions

Drug hypersensitivity reactions (DHRs) are adverse effects of drugs that **clinically resemble** allergic reactions

Drug allergies are DHRs for which a definite immunological mechanism (either drug-specific antibody or T cell) is demonstrated

DHRs may be allergic or nonallergic

Nonallergic DHRs resemble allergy, but without any proven immunological mechanism

-life-threatening

-may require or prolong hospitalization

-may necessitate changes in subsequent therapy

WAO

- Type A reaction- overdoses and pharmacological reactions, dose dependent and predictable

- Type B reaction-dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans

Epidemiology

ADRs account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients

Drug allergy is relatively uncommon, accounting for less than 10% of all ADRs

Drug allergy, occurs in 1% to 2% of all hospital admissions and 3% to 5% of hospitalized patients

The true incidence of drug allergy in the community, and among children and adults, is unknown.

Risk Factors

Drug dependent

Nature of the drug

Degree of exposure (dose, duration, frequency)

Route of administration-oral administration of a drug is generally safer than any type of parenteral administration

Cross-sensitization

Risk Factors

Other

Age and Sex

Genetic factors

Concurrent medical illness

Previous drug reaction

Multiple allergy syndrome

Pathogenesis and pathophysiology

Numerous reactions with symptoms suggestive of allergy are often erroneously considered to be real drug allergies with suggested mechanisms:

- nonspecific mast cell or basophil histamine release (e.g., opiates, radiocontrast media, and vancomycin)
- bradykinin accumulation (angiotensin-converting enzyme inhibitors)
- complement activation (e.g., protamine)
- alteration in arachidonate metabolism (e.g., aspirin and nonsteroidal anti-inflammatory drugs)
- the pharmacological action of certain substances inducing bronchospasm (e.g., β-blockers)

Pathogenesis and pathophysiology

IgE-mediated reactions

Drug allergens bind to IgE antibodies, which are attached to mast cells and basophils, resulting in IgE cross-linking, cell activation and release of preformed and newly formed mediators (e.g., urticaria, angioedema, anaphylaxis)

Non-IgE-mediated reactions

-Cytotoxic/cytolytic reactions involving the interaction of IgG or IgM antibodies and complement with a drug allergen associated with cell membranes (e.g., immune hemolytic anemia, thrombocytopenia)

-Drug immune complex reactions (e.g., serum sickness and drug-induced lupus)

-T-cell–mediated reactions

Role of viruses in the pathogenesis of DHRs

Viral infections can lead to skin eruptions and mimic DHRs if a drug (mostly an antibiotic) is taken at the same time

Viral infections can also interact with drugs, leading to mild eruptions in the case of the ‘ampicillin rash’ linked to the EBV infection

Clinical Classification of DHRs

Immediate DHRs- typically 1-6 h after the last drug administration

Urticaria Angioedema

Rhinitis Conjunctivitis

Bronchospasm Anaphylaxis

Gastrointestinal symptoms (nausea, vomiting, diarrhea)

Clinical Classification of DHRs

Nonimmediate DHRs

Delayed urticaria

Maculopapular eruptions

Fixed drug eruptions

Vasculitis

Toxic epidermal necrolysis

Stevens–Johnson syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Acute generalized exanthematous pustulosis

Symmetrical drug-related intertriginous and flexural exanthemas

Nonimmediate DHRs

Internal organs can be affected either alone or with cutaneous symptoms-they may occur at any time as from 1 h after from the initial drug administration

Hepatitis

Pneumonitis

Neutropenia

Renal failure

Anemia

Thrombocytopenia

Drug-induced hypersensitivity syndrome

1. Maculopapular rash developing ≥3 weeks after starting therapy with a limited number of drugs
2. Lymphadenopathy
3. Fever (≥38°C)
4. Leukocytosis (≥10 ´ 10^9/L), atypical lymphocytosis or eosinophilia
5. Hepatitis (alanine aminotransferase [ALT] ≥100 U/L)
6. Human herpes virus (HHV)

Diagnosis

Clinical history

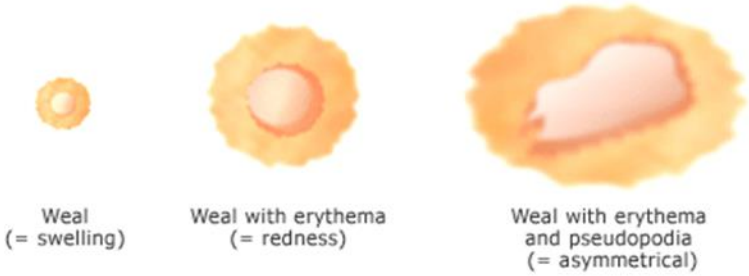
Standardized skin tests

In vitro tests

Drug provocation tests

Skin prick test

A positive SPT is defined as mean weal diameter >3 mm (associated with a flare response) compared to the negative control after 15 to 20 minutes



Skin Prick -Technique

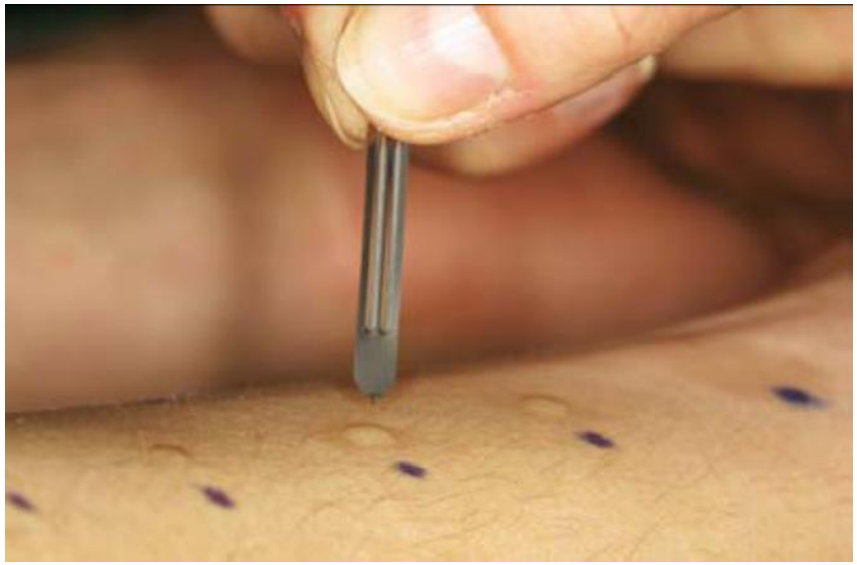
In performing the skin prick test, a drop of allergen extract is placed on the skin, then pierced through by the instrument at a 45–60° angle to the skin, creating a small break in the epidermis, which allows the allergen solution to penetrate.

Skin Prick -Technique

This technique should not cause bleeding

The excess extract is removed with gauze or tissue paper

A variation of this is the puncture method, in which the device is held at a 90° angle to the skin and pushed through the extract into the epidermis.



Intradermal Test

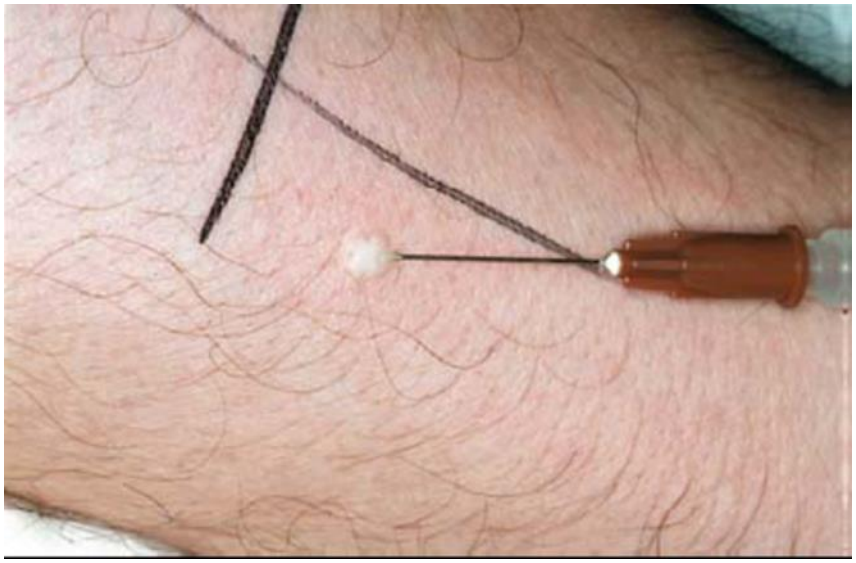
IDTs are performed only when prick tests show negative results 20 min after testing with the suspected drug

Compared to skin prick tests, they provide an enhanced sensitivity for drug-specific IgE

They should be performed with the intravenously injectable form of the drug whenever possible

Intradermal Test

An IDT is accomplished by injecting 0.02 to 0.05 mL of an allergen intradermally, raising a small bleb measuring 3 mm in diameter



Intradermal Test

The IDT is more sensitive than the SPT, but also carries a higher risk for inducing an irritative, falsely positive reaction and might even lead to anaphylaxis in IgE-dependent reactions. Readings should be taken after 15 to 20 minutes for evaluation of immediate reactions, and after 24 and 72 hours for evaluation of nonimmediate (late) reactions.

Patch Tests

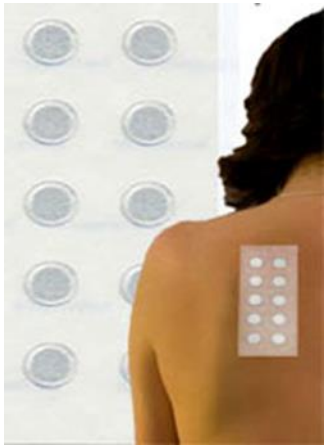
If the commercialized form of the drug is tested, pills must have their coating removed

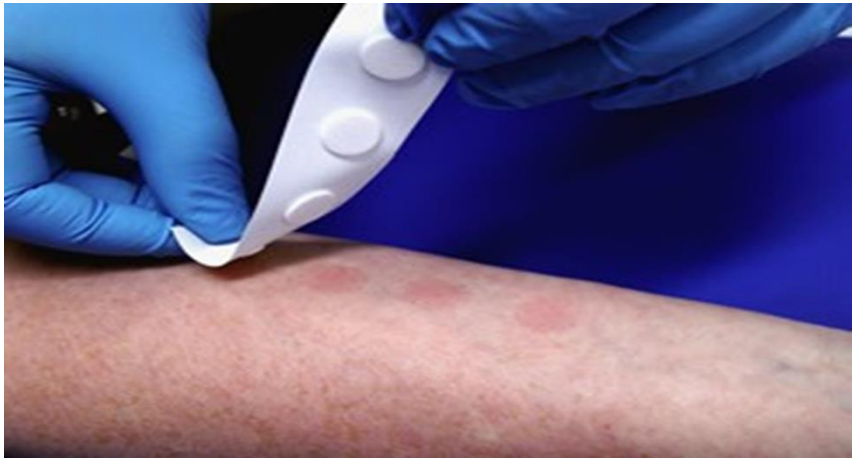
The substance has to be smashed to a very fine powder

The powder contained in capsules is tested at 30% in petrolatum and at 30% in water

Liquid preparations are tested both as is and diluted at 30% in water

Patch testing with Finn chambers





In Vitro Tests

Serum total tryptase levels

Allergen-specific IgE levels:

- radioallergosorbent tests (RASTs)
- radioimmunoassay (RIA)

Flow cytometry–based basophil activation assays-levels of CD63 and CD203c

Drug provocation (challenge) tests

DPT involves administering the drug using slow, incremental dose escalations at fixed time intervals and observing for the presence or absence of an objective reaction

It is not without risk to the patient and should be done only under the strict supervision of clinicians/nurses with allergy training and with resuscitative equipment available

Treatment

Mild reactions: antihistamines

Anaphylaxis: emergency management, including securing the airway; maintaining breathing and circulation; and use of drugs:

- Intramuscular epinephrine 0.3 mL of a 1:1,000 concentration up to every 5 minutes in adults or 0.01 mg/kg in children up to a maximum dose of 0.3 mg
- Intramuscular promethazine or intravenous diphenhydramine
- Intravenous fluids (colloids or crystalloids)

Specific Treatment

Drug Desensitization

Desensitization is a process in which the drug to which the patient is allergic is administered to the patient in small, incremental doses to induce a state of temporary tolerance to the drug

Regimes have been described for many drugs including penicillins, cephalosporins, cotrimoxazole, allopurinol and the chemotherapeutic agents

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Severe adverse reactions to drug, characterized by the widespread destruction of the epithelium of the skin and mucous membranes

SJS and TEN are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions

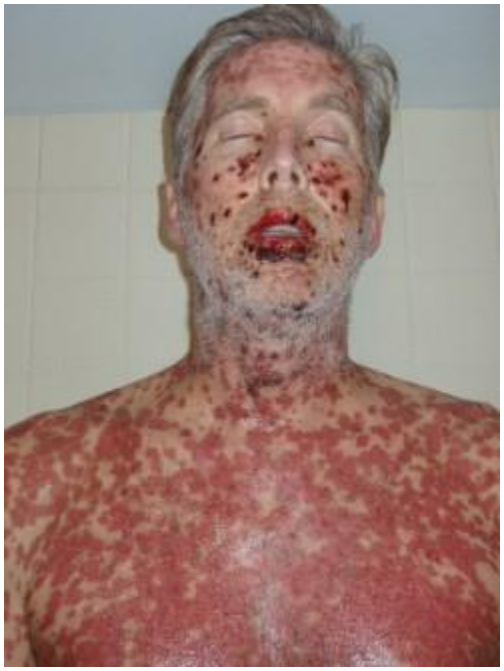
Both are considered medical emergencies as they are potentially fatal

Epidemiology

Incidence rates for SJS, TEN and their overlap are 1–2 cases per 1 million population per year

When the area of affected skin is less than 10% (SJS), the mortality rate is 1 to 5%

If it is more than 30% (TEN), the mortality rate is between 25% and 35% and may approach 50%



Etiology

Allopurinol

Aminopenicillins

Quinolones

Carbamazepine

Phenobarbital

Sulfonamide- antibiotics

Cephalosporins

Chlormezanone

Phenytoin

Allopurinol

Non-steroidal antinflammatory drugs of the oxicam-type

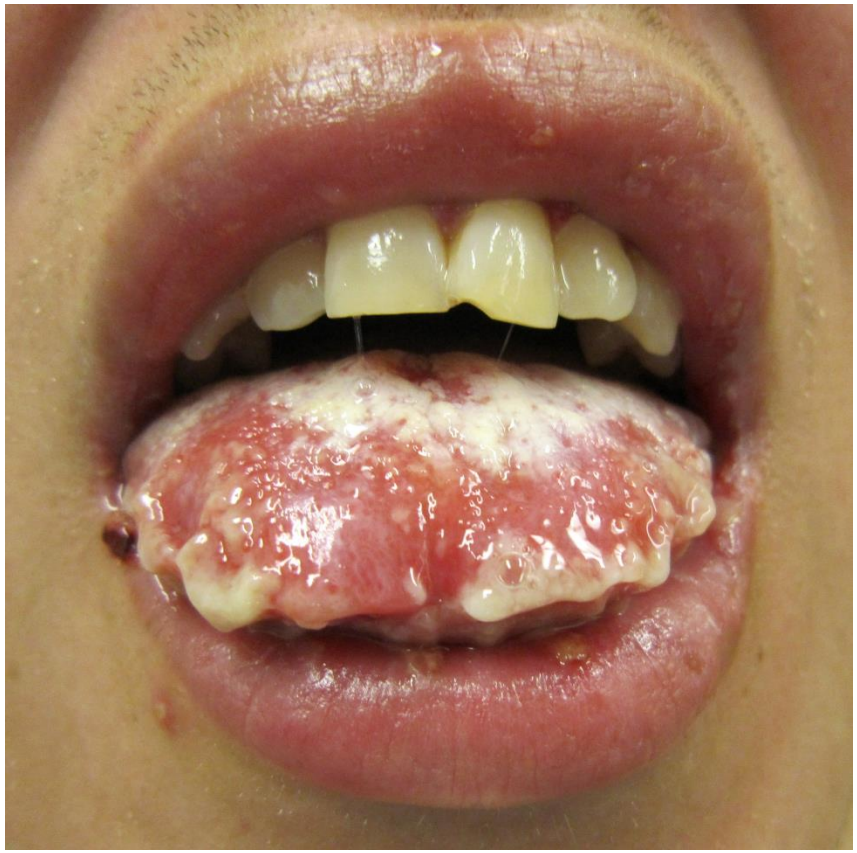
Clinical Manifestation

Acute Phase

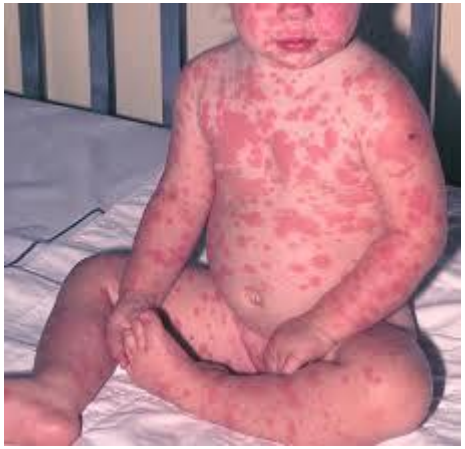
Fever, stinging eyes and discomfort upon swallowing precede cutaneous manifestations by a few days

Cutaneous involvement-presternal region of the trunk and face, palms and soles

Buccal, genital and/or ocular mucosa involvement in more than 90% of patients



Clinical Manifestation



Skin lesions

Erythematous and livid macules- early

Large areas of epidermal detachment-second phase

Necrotic skin-blisters, erosions

Clinical Manifestation

Ocular involvement

Acute conjunctivitis
Eyelid edema

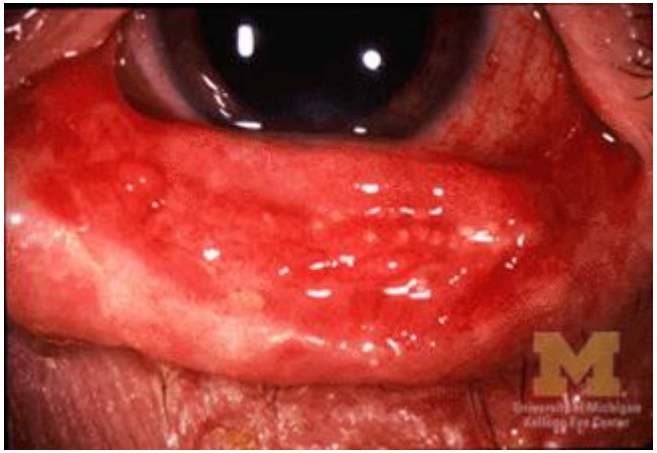
Erythema
Crusts

Ocular discharge

Conjunctival membrane or pseduomembrane formation

Corneal erosion
Cicatrizing lesions

Corneal ulceration



Clinical Manifestation

Late Phase

Hyper- and hypopigmentation of the skin

Nail dystrophies

Late ocular complications-severe dry eyes, trichiasis, visual loss, entropion

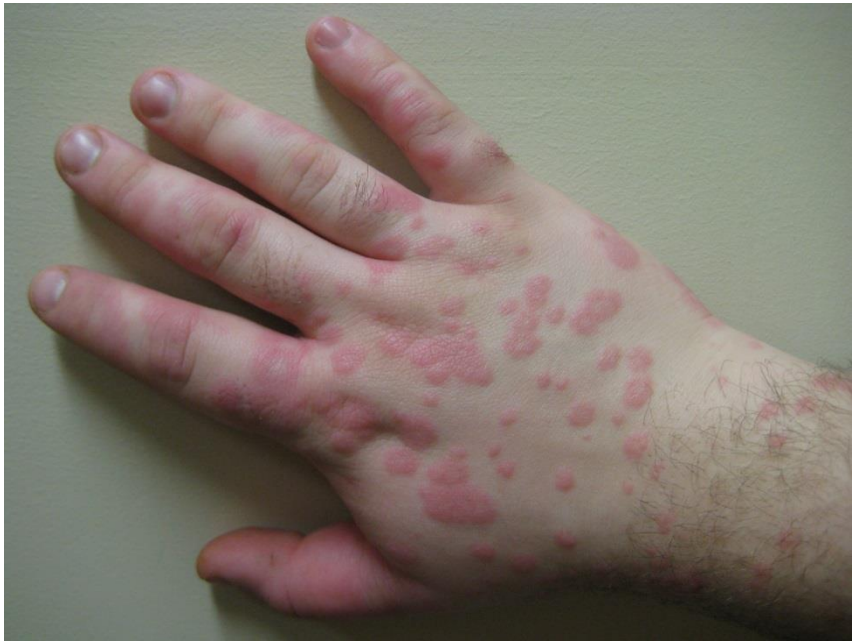
Diagnosis

Typical clinical signs

Histological features

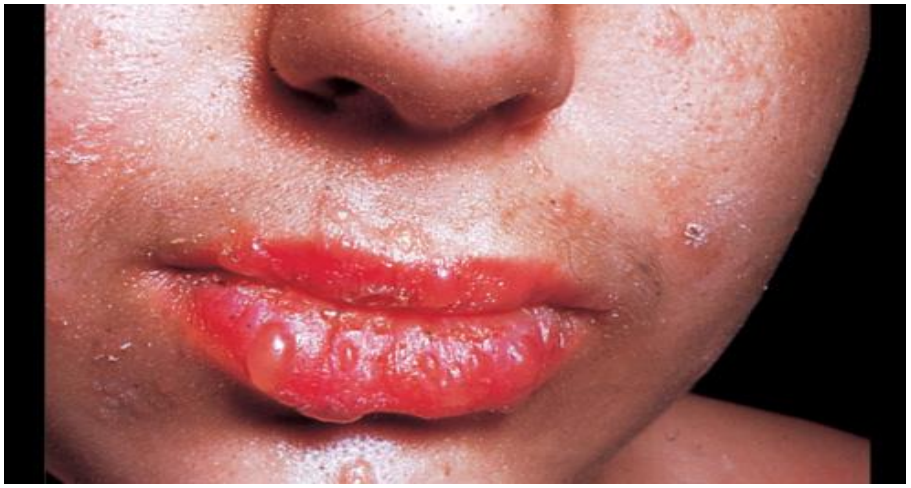
Mucosal, including ocular, involvement develops shortly before or simultaneously with skin signs in almost all cases.

Differential Diagnosis



Erythema multiforme (EM) is a more benign condition with target and targetoid lesions usually in an acral distribution with involvement of less than 10% of the skin and commonly with oral involvement

Most cases are secondary to herpes simplex infection and recur with herpetic recurrences.



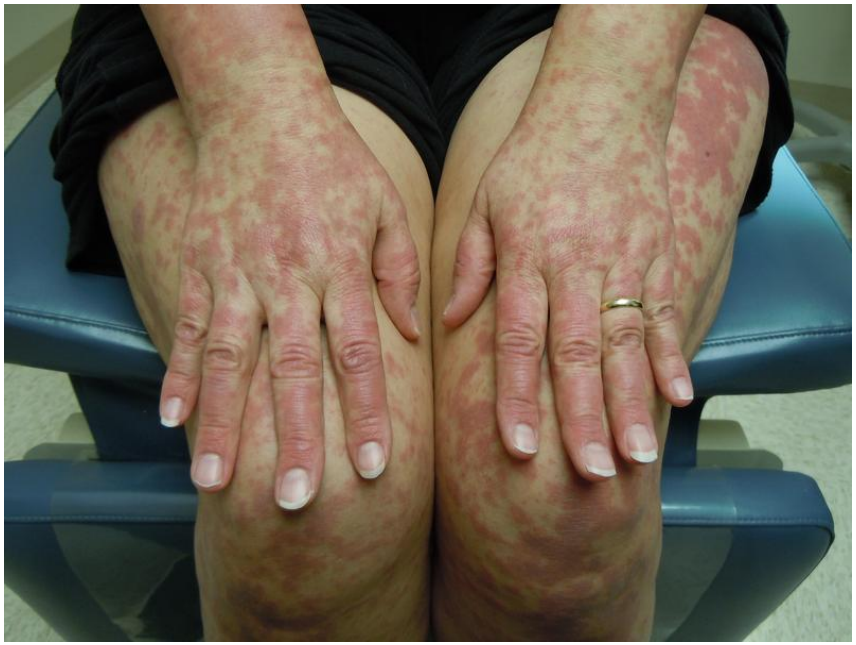
Differential Diagnosis

Common Associations

HSV

Mycoplasma

Drugs only about 10% overall, with NSAIDs and sulphonamides commonest causes



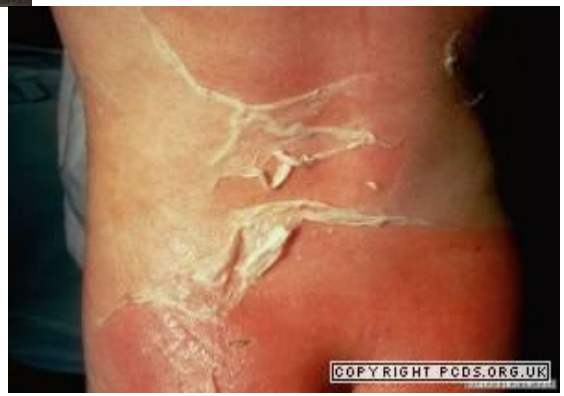
Differential Diagnosis

autoimmune blistering diseases

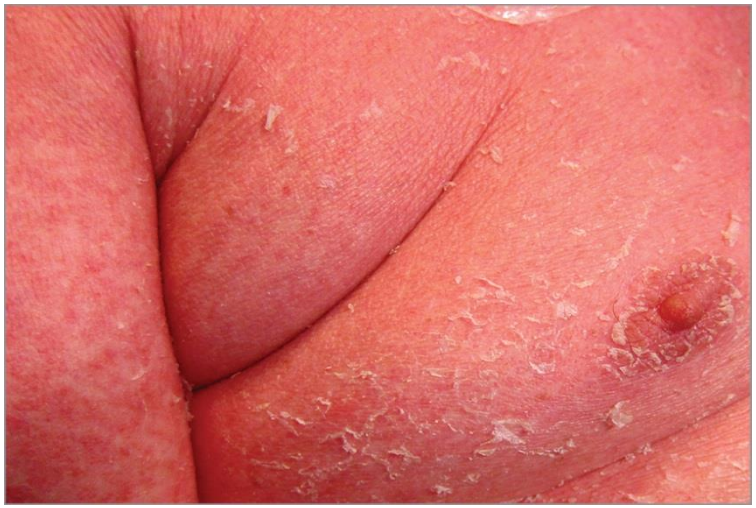
-linear IgA dermatosis

-paraneoplastic pemphigus

-pemphigus vulgaris



staphyloccocal scalded skin syndrome



Treatment in acute stage

Patients should be managed in an intensive care unit if possible.

Prompt withdrawal of culprit drug(s)

Supportive Care

- Intravenous fluid with 0.5% NaCl
- -Replacement therapy in case of hyponatraemia, hypokalaemia or hypophosphataemia

-Wounds should be treated conservatively, without skin debridement which is often performed in burn units

-Nonadhesive wound dressings

Drug Therapy

-Systemic steroids

-High-dose intravenous immunoglobulins with appropriate precaution in patients with potential risk factors (renal insufficiency, cardiac insufficiency, IgA deficiency, thrombo-embolic risk)

-Ciclosporin (CsA)-calcineurin-inhibitor

-TNF antagonists

- Plasmapheresis/plasma exchange

Treatment of sequelae

-Prevention of ocular complications

-Treatment with topical steroids

-Hypopharyngeal stenosis combined with dysphagia and oesophageal strictures are long-term complications which are difficult to treat and may require laryngectomy.

Allergy to Anesthetic Agents

Two types of reactions

1. Dose-dependent and related to the pharmacological properties of the drug and/or its metabolites

2. Unrelated to the drug's pharmacological characteristics and that are less dose-dependent

- drug intolerance
- idiosyncratic reactions
- drug-induced immune-mediated allergic reactions
- nonimmune-mediated pseudo-allergic or anaphylactoid reactions

Prevalence

The use of anesthetic agents and drugs during anesthesia induces a certain number of anaphylactoid reactions

The incidence of anaphylaxis lo intravenous agents used during general anesthesia is about 1/5000

The estimated incidence of immediate hypersensitivity reactions from all mechanisms ranges from one in every 1,250 to 10,000 anesthetics

Pathophysiology

IgE-mediated anaphylaxis

Neuromuscular blocking agents (NMBAs) represent the most frequently substances responsible for IgE-mediated anaphylaxis

suxamethonium
atracurium
rocuronium
cisatracurium
vecuronium
pancuronium
mivacurium

Hypnotic agents, opioids, colloids, aprotinin, protamine are less frequently incriminated for IgE-mediated reactions

Allergy to local anesthetics is rarely reported

Non-allergic anaphylaxis

-atracurium and mivacurium are histamine-releasing drugs

-cisatracurium does not have histamine-releasing effects

Nonspecific histamine-release : thiopental, morphine and vancomycine in response to the injection of rapid high concentrations of these substances

Diagnosis of a Perioperative Anaphylactic Reaction

Any suspected hypersensitivity reaction during anesthesia must be extensively investigated using combined pre and postoperative testing

Immediate investigations

-serum tryptase-high tryptase levels strongly suggest an immunological mechanism.

-plasma histamine determinations

-specific IgE assays

Secondary investigations

Skin tests-combined with history, remain the mainstay of the diagnosis of an IgE-mediated reaction (4 to 6 weeks after a reaction)

If necessary, skin tests can be performed earlier with all the drugs used in the anesthetic procedure, as well as with latex and any other drugs or products administered during the anesthesia, apart from agents administered by inhalation

Skin prick-tests (SPT) and intradermal tests (IDT) with dilutions of commercially available drug preparations are advised

Advice to patients

In order to make subsequent anesthesia as safe as possible, a close collaboration between allergologist and anesthesiologist is highly desirable

At the end of the allergic work-up, the patient should be warned against any substance which has tested positive, and a warning card or bracelet should be issued

A detailed letter containing information on the reaction, on the drugs given, on the results of follow-up investigations and advice for future anesthetics should be issued to the patient, the referring anesthesiologist and the patient’s general practitioner

Contrast Medium Reactions

Organic radiographic iodinated contrast media (ICM) have been among the most commonly prescribed drugs in the history of modern medicine

ICM are chemical modifications of a 2,4,6-tri-iodinated benzene ring

Types of Iodinated Contrast Media

In clinical practice, categorization based on osmolality is widely used

-High-osmolality contrast media

-Low-osmolality contrast Media

There are 3 types of low-osmolality ICM

-Nonionic monomers

-Ionic dimers

-Nonionic dimers

Adverse Reactions to ICM

Idiosyncratic Reactions-typically begin within 20 minutes of the ICM injection, independent of the dose that is administered. A severe idiosyncratic reaction can occur after an injection of less than 1 mL of a contrast agent. Immunoglobulin E (IgE) antibodies are not involved.

Idiosyncratic reactions to ICM are called anaphylactic reaction: mild, moderate, severe symptoms

Nonidiosyncratic Reactions

Bradycardia, hypotension, and vasovagal reactions

Nephropathy

Cardiovascular reactions-hypotension and bradycardia

Extravasation

Delayed reactions-30 minutes after but within 7 days of the ICM injection

Common delayed reactions include:

fatigue, weakness, upper respiratory tract congestion, fevers, chills, nausea, vomiting, diarrhea, abdominal pain, pain in the injected extremity, rash, dizziness, and headache

These signs and symptoms almost always resolve spontaneously; usually, little or no treatment is required. Some delayed reactions may be coincidental.

Treatment of Adverse Reactions

Anaphylactic Reactions

Urticaria: diphenhydramine 50 mg may be administered orally, intramuscularly, or intravenously

Bronchospasm: For mild bronchospasm, treatment includes oxygen 10-12 L by face mask, close observation, and/or 2 puffs of an albuterol inhaler

For moderate cases without hypotension, treatment is as above, with epinephrine 1:1000, 0.1-0.3 mL given subcutaneously, repeated every 10-15 minutes as needed until 1 mL is administered.

In patients with severe bronchospasm, administer epinephrine 1:10,000 1 mL slow intravenous injection over approximately 5 minutes, repeated every 5-10 minutes as needed

Isolated hypotension: Raise the patient's legs as much as possible while preparing to administer intravenous fluids. The Trendelenburg position can also be effective, but many radiographic tables do not tilt. Oxygen should be administered in high doses.

Vasovagal reaction

In cases of mild to moderate vasovagal reactions elevate the patient's legs. Administer oxygen 10-12 L by face mask, and intravenous isotonic fluid (eg, 0.9% isotonic sodium chloride solution, Ringer lactate solution)

For severe reactions or unresponsive patients, administer intravenous atropine 0.6-1 mg, repeated every 3-5 minutes as needed until a total of 3 mg is administered

Treatment of Nonidiosyncratic Reactions

Vasovagal reaction

Hypotension resulting from a vasovagal reaction is treated with iso-osmolar fluid

If the patient remains symptomatic, bradycardia can be reversed with intravenous atropine 0.6-1 mg, repeated every 3-5 minutes to a total dose of 3 mg, if needed

Cardiac arrhythmias

A defibrillator should be obtained and cardioversion or defibrillation should be performed.

Hypertensive reactions

Hypertensive reactions can be initially treated with oxygen and appropriate antihypertensive medications. Additional doses of the patient's usual antihypertensive medications may be helpful

Delayed reactions

Analgesics are administered to treat headaches; antipyretics to treat high temperatures; and isotonic fluid for hypotension

Extravasation injuries

Elevating the affected extremity and applying cold compresses


Thank
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