
بسم الله الرحمن الرحیم

دانشگاه علوم پزشکی و خدمات بهداشتی درمانی استان مرکزی

عوارض دارو های تزریقی
عوارض پوستی داروها
ازدیاد حساسیت و شوک آنافیلاکسی

واحد تحقیق و توسعه

معاونت غذا و دارو اراک

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Adverse effect of injectable medicine

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- 95%:curative injection
- 3-10%:imunization
- 1%:injectable contraceptive
- 1%blood and blood pruduct

  16 thousand milion injection

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Problems of injections

- Dangerous engine of disease
- cause more serious adverse events
- Need more personal and equipment
- Are more expensive

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Reported injectable medicines commonly used

- Antibiotics
- Antiinflammatory agents
- vitamins

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Reported factors leading to injection over use

- Prescriber-associated factors

  -prescription regarding injection

  -assumption about patients expectations
- Patient-associated factor

  -Perceptions regarding injections

  -therapeutic expectation
- System issues

  -lack of effective oral medications

  -financial implication

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Reported prescribers' reasons for the use of injections

- Pharmacokinetics
  - "Strength" of injectables
  - Rapid onset of action
  - Poor intestinal absorption of oral medications
  - Absence of effective oral medications
- Other
  - Recommendations by Professors/Ministry of Health
  - Direct observed therapy
- Patient care issues
  - Inability of patient to take medications by mouth
  - Patient's desire for injection
  - Chronic condition of patient (illness, malnutrition or alcohol abuse)

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Peak serum concentration of selected oral, IM and IV antibiotics

Class of Antibiotic	Oral	IM	IV
Natural Penicillin	++	-	+++++
Aminopenicillin	+	++	+++
Fluoroquinolones	+	NA	+
Chloramphenicol	++	+	++
Sulfonamides	+	NA	+
Rifampin	+	NA	++

Source: Micromedex

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Time to peak serum concentration by different modes of administration

- Oral
  - 30min – 6hrs
- IM
  - 30min – 3hrs*
- IV
  - End of infusion

* Natural penicillin time to peak serum concentration 4-24 hrs

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Compared cost of selected oral and parenteral antibiotics

Drug	Relative cost of parenteral:oral per equivalent Dose
Ampicillin	3:1
Cloxacillin	4:1
Chloramphenicol	5:1

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Comparison of the phamacokinetics of different NSAIDs by route of administration

Class	NSAID	Bioavailability (%)		Time to serum peak (hours)	
		Oral	IM	Oral	IM
Salicylic	Aspirin	80-100	NA[1]	0.5-3	NA
	Lysine Acetylsalicylate	---	NA	1-2	0.25
Indolic	Indometacin	90-100	NA	0.5-2	NA
Aryl-carboxylic	Ketoprofen	95-100	NA	0.5-2	0.3-0.5
	Ibuprofen	80	---	2	---
	Diclofenac Na	100	100	1.5-3	0.3
	Ketorolac	80-100	100	0.3-1	0.5-1
Oxicam	Naproxen	100	---	1-2	---
	Piroxicam	100	---	3-5	NA
	Isoxicam	100	100	10	3
Fenamates	Meloxicam	89	---	1	NA
	Niflumic ac.	---	---	2	---
Pyrazolic	Phenylbutazone	100	---	2-5	NA

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Compared outcomes of oral and IM administration for selected vitamins

Vitamin	Number of Studies	Outcome Equal Oral and IM
B6	0	NA
B12	1	1/1 @
K	2	1 / 2 *

@ clinical outcome *Markers of Vitamin K status

Conclusions (1)

- There is minimal to no benefit of IM versus oral administration of drugs in terms of pharmacokinetics
- IV administration results in shorter onset of action and for some drugs higher bioavailability and peak serum levels
- The issue of onset of action is clinically relevant only in life threatening illness

Conclusions (2)

- The pharmacokinetic advantage of parenteral over oral drugs does not translate to better clinical outcomes in mild-moderate illness
- Even in serious illnesses, sequential therapy within 2-5 days can be as effective as prolonged parenteral courses

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Recommendations: indication for therapeutic injections

- Serious and life-threatening illness
- Inability to swallow
- Profuse vomiting
- Absence of effective oral agent
- Significantly altered absorption pattern

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How can we reduce the adverse reaction of injectable drug?

- Indication
- Check the leaflet
- Same appearance
- Counterfeit medicine
- Maintenance
- Preparation
- Rate of injection

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شایعترین داروهای مسبب عارضه

رتبه	دارو	تعداد	درصد
۱	سفتریاکسون	۱۴۶۰	۱۴
۲	وانکومایسین	۷۸۷	۷
۳	سفازولین	۶۷۰	۶
۴	استرپتوکیناز	۶۴۰	۵/۸
۵	هیدروکورتیزون	۵۶۵	۵
۶	پنی سیلین	۴۵۰	۴/۱
۷	دیکلوفناک	۴۴۲	۴/۰۴
۸	ترامادول	۴۴۰	۴/۰۲
۹	دفروکسامین	۴۳۰	۳/۹۳
۱۰	دگزامتازون	۳۳۰	۳/۰۲

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Cutaneous drug reaction

- Drug eruption:

  age

  diagnosis

  severity of illness

  sex

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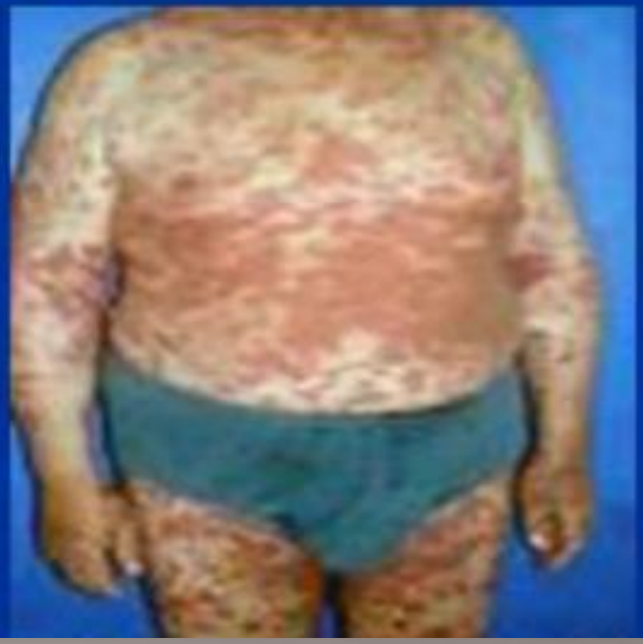
- Skin reactions : the most common ADRs
- About 5% of hospitalizations in dermatology departmens
- Approximately 10% of drug eruptions are **severe** (hospitalization, and even life-threatening)

Exanthematous Drug Eruptions

Appearance	Begin as macules, can develop into papules. Two forms: Morbilliform, Scarlatiniform
Differential Diagnosis	Viral exanthems
Time from drug administration to onset	• Sudden onset during the 1st two weeks of drug therapy; semisynthetic penicillins after the first 2 weeks. • Recurs on re-challenge.



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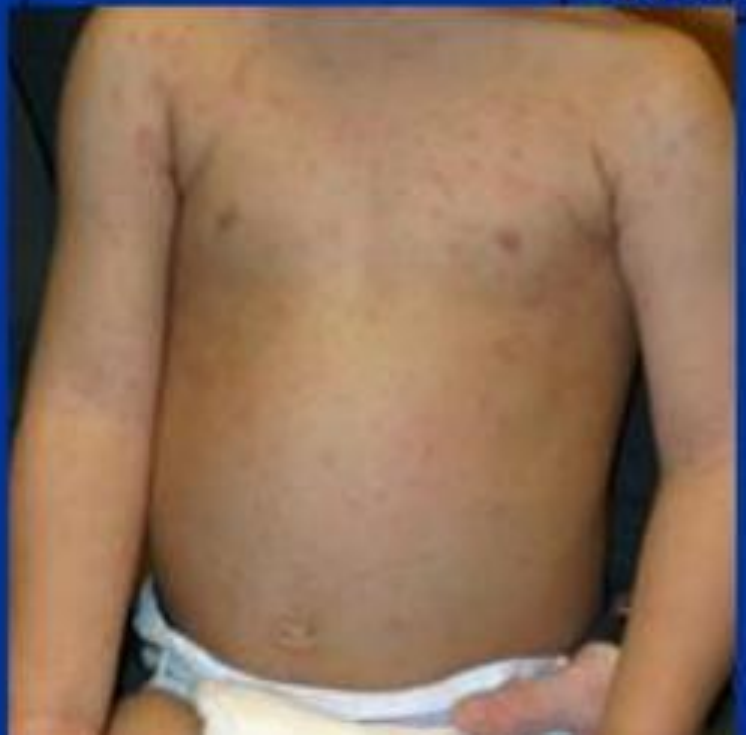
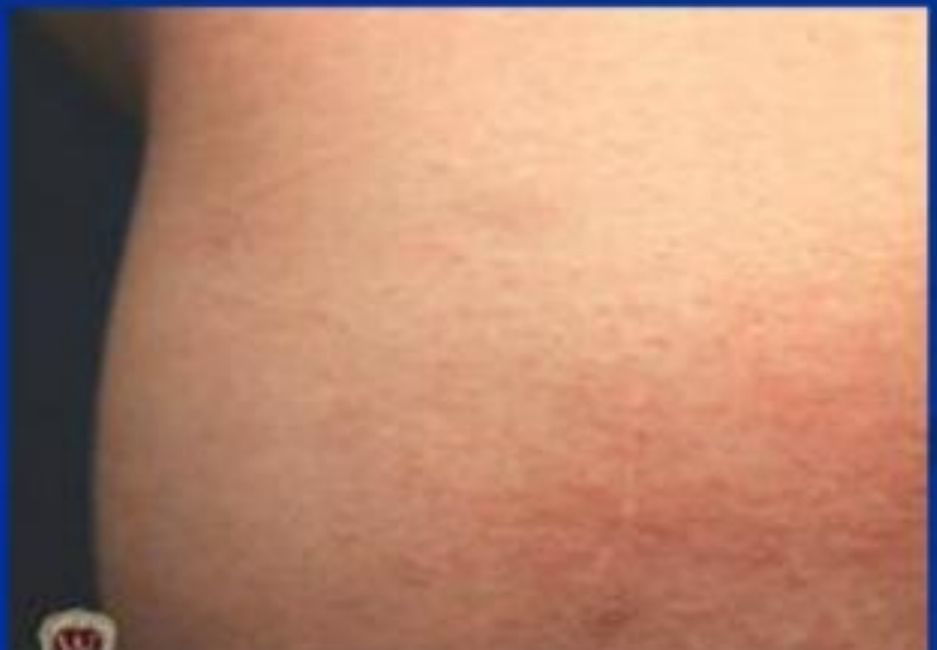
Exanthematous Drug Eruptions

Commonly implicated drugs

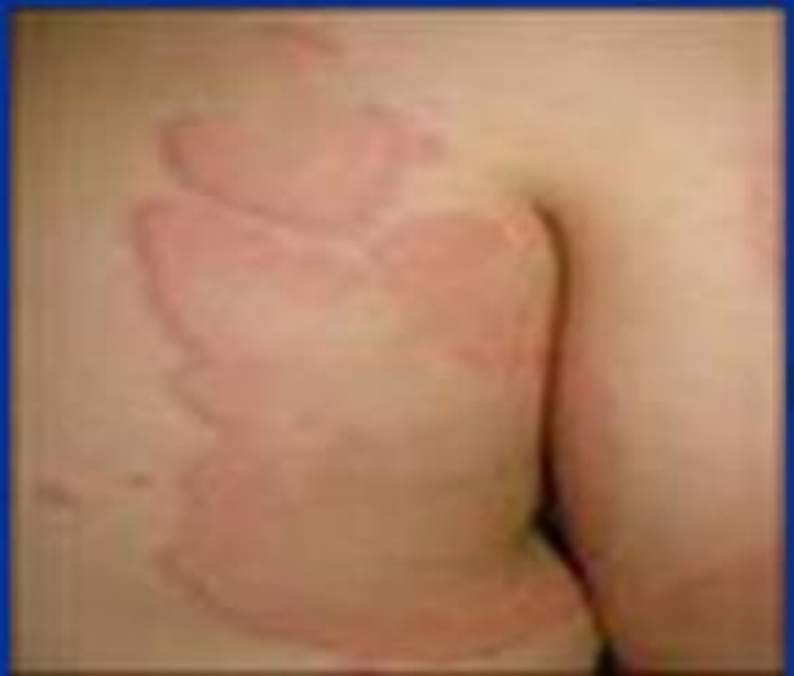
- Phenytoin
- Carbamazepine
- Penicillin family of drugs (aminopenicillins)
- NSAIDs
- Sulfonamides
- Antituberculous drugs
- Phenobarbital





Urticaria (Hives)

- Urticaria mechanisms
  - IgE-dependent
  - Circulating immune complexes (serum sickness)
  - Nonimmunologic activation of effector pathways



Urticarial Drug Eruptions (2)

Pathogenesis	Early Type I hypersensitivity reaction or drug stimulation of mast cells.
Risk Factors	Atopic diathesis (allergies, asthma), viral infection with commonly associated drug
Treatment	•Discontinue drug •Oral antihistamines and systemic corticosteroids helpful •Emollients during resolution
Resolution	Re-challenge based on severity of the reaction. Avoid in anaphylaxis. De-sensitization procedures available.

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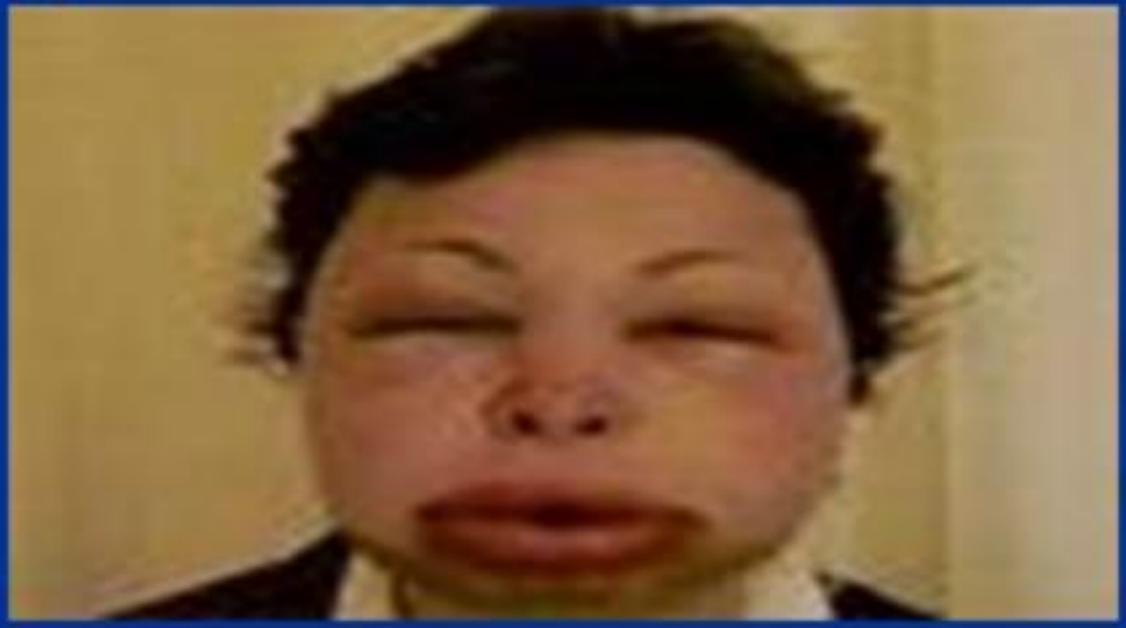
Urticarial Reaction

In **penicillin-induced urticaria**, the risk of crossreactivity with another betalactam is estimated to be between **10 and 20%.**

So, an **antibiotic of a different class** should be used when possible.

Angioedema

- Deep dermal and subcutaneous tissues are swollen
- May involve mucous membranes
- May be part of a life-threatening anaphylactic reaction
- Onset: hours-days; can develop after long-term use
- Triggers: drugs, foods, insect bites, emotional stress
- Known drugs: ACE inhibitors (0.1-0.5%), losartan, donepezil,



Angioedema

- Treatment:
  - Mild
    - Withdraw medication: resolve within hours
    - Cool compresses or soaks for pain relief
  - Difficulty breathing/stridor
    - Antihistamines, epinephrine, corticosteroids

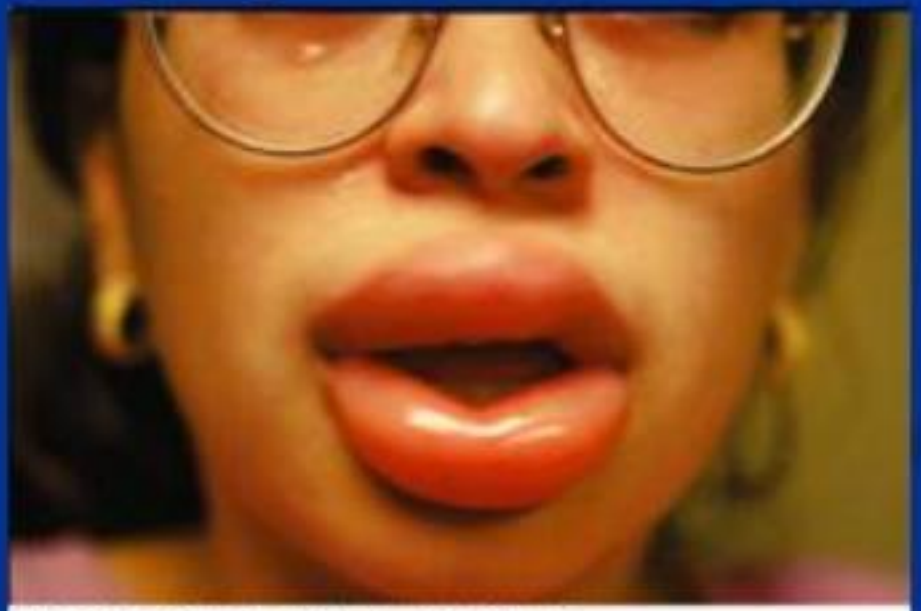

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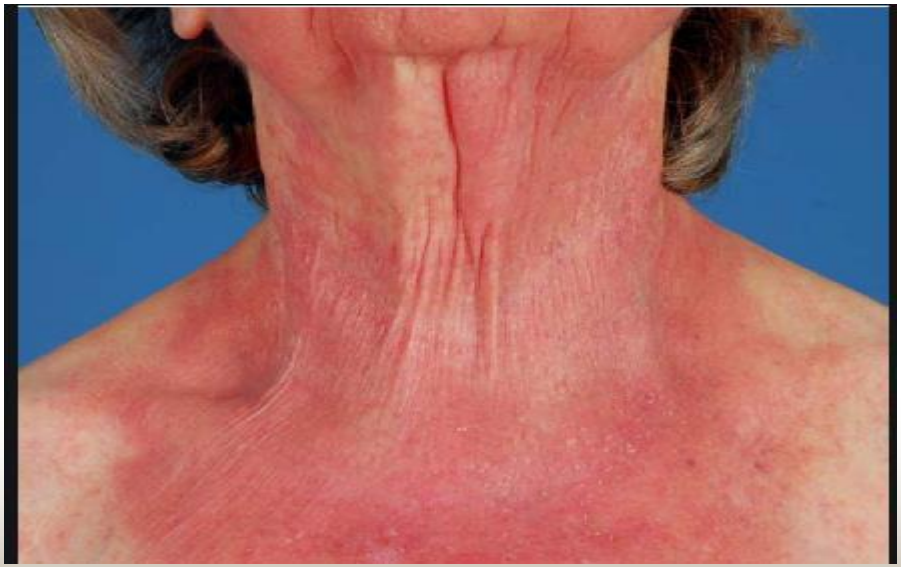
Photo sensitivity

- Appears in sun-exposed areas
- Phototoxic:dose dependent,resemble sunburn,pruritis possible
- Photo alergic:eczematous,pruritic,requires sensitization



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Photosensitivity Reactions (2)

Commonly implicated drugs

Phototoxic:

- Tetracyclines
- Fluoroquinolones
- Amiodarone
- Psoralens (in coal tar preparations)
- Griseofulvin
- Diuretics (furosemide and thiazides)
- NSAIDs (ibuprofen)
- Antipsychotics (chlorpromazine, prochlorperazine)
- St. John's Wort

Photoallergic:

- Sunscreens, fragrances, antibacterial agents, latex
- Thiazide diuretics
- Griseofulvin
- Quinidine
- Sulfonamides
- Sulfonylureas
- Pyridoxine (vitamin B_6)

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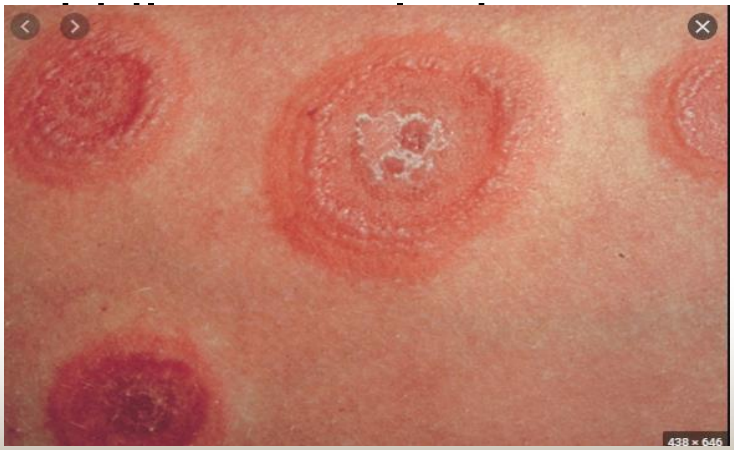
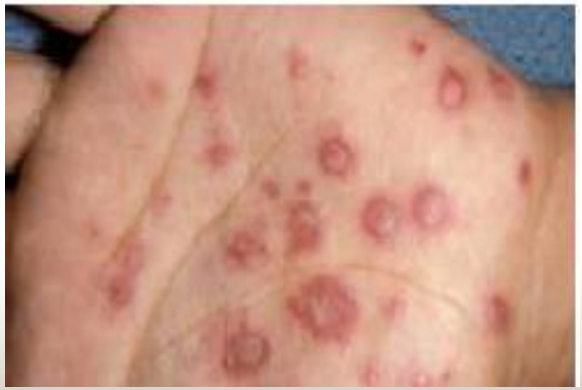
Erythema multiform

- 90% cases:herpes simplex virus or drug reactions
- Onset:days-weeks
- Variety of morphologic forms
- ➢ Erythematous,iris-shaped papules and vesicolobullouslesions
- ➢ Appearance of circular target with bulls-eye in the





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Erythema multiform

- Typicaldrugs:NSAID,sulfunamides,phenothiazine,barbiturates,allopurinol
- Treatment:self-limiting 2-3 weeks

➢ Mild:supportive-viscouslidocaine,analgesic ,hydration

➢ Moderate-severe:oral corticosteroids

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Stevens johnson syndrome & TEN

- Stevens-Johnson syndrome(SJS) and toxic epidermal necrolysis (TEN) have traditionally been considered the most severe forms of erythema multiform(EM).

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Stevens johnson syndrome & TEN

- A three-grade classification has been proposed:
  - Grade 1:SJS mucosal erosions and epidermal detachment below 10%
  - Grade 2:Overlap SJS/TEN epidermal detachment between 10% and 30%
  - Grade 3;TEN epidermal detachment more than 30%

Stevens johnson syndrome

- Vesiculobullous disease of the skin,mouth,eyes,and genitals
- The disease occurs most often in children and young adults.

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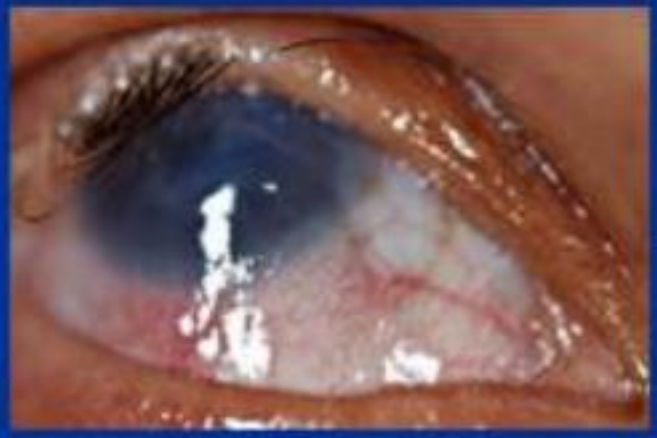
Stevens-johnson syndrome

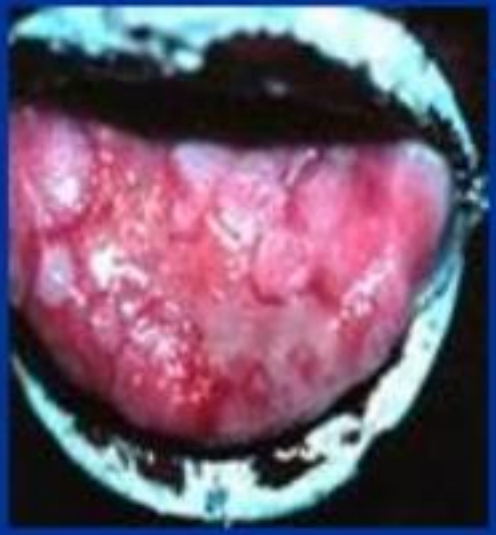
- Skin lesions: flat atypical targets or purpuric maculae(trunk,palms,soles)
- Mucosal lesions:Bullae (conjunctivae,mucous membranes of the nares,mouth,anorectal junction,vulvovaginal region and urethral meatus Ulcerative stomatitis leading to hemorrhagic crusting is the most characteristic
- Ocular symptoms:corneal ulcerations may lead to blindness.

Stevens johnson syndrome

- Diagnosis:A skin biopsy should be performed if the classic lesions are not present.
- Treatment:Corticosteroids,Antihistamines, wet Burrow's compress.

Stevens-Johnson Syndrome





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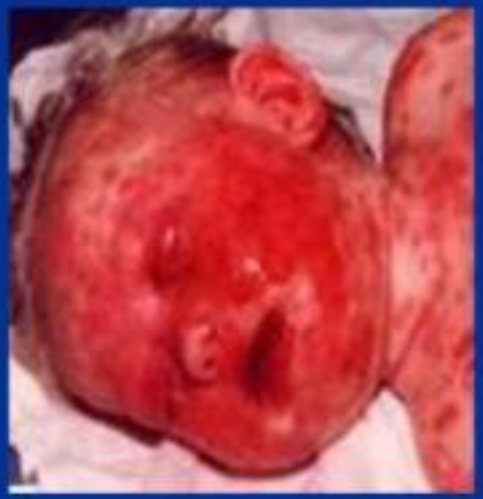
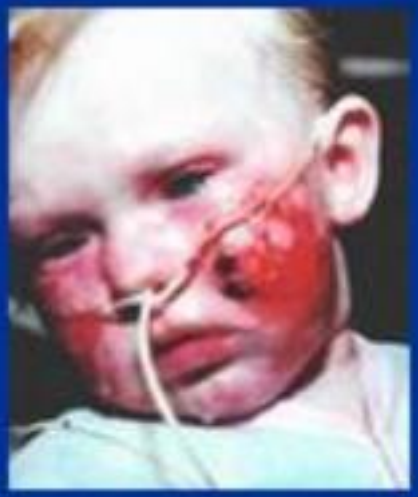
Stevens-Johnson Syndrome

- Small blisters on dusky purpuric macules or atypical targets
- Detachment <10% of body surface area
- 10-30% involve fever
- Duration 4 to 6 weeks
- Mortality 5 to 18%
- Typical drugs: allopurinol, carbamazepine, fluoroquinolones, sulfonamides
- Treatment: supportive





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Stevens-Johnson Syndrome

- Etiology:Drugs are the most common cause (Phenytoin,Phenobarbital,sulfonamides, penicillins)

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Stevens-Johnson Syndrome

- The disease occurs most often in patient treated for seizure disorders.
- URI ,GI disorders,Mycoplasma pneumoniae infection,and Herpes simplex virus infection are all implicated.

Stevens-Johnson Syndrome Total 228

Drug Name	NO.	Drug Name	No.
Lamotrigine	49	Nevirapine	1
Carbamazepine	39	Clarithromycin	1
Co-Trimoxazole	39	Captopril	1
Phenobarbital	24	Piroxicam	1
Phenytoin	23	Dipyridamole	1
Penicillin	11	Novafen	1
Ceftriaxone	6	Imipramine	1
Ampicillin	4	Mefenamic acid	1
Cefixime	3	Valproate Na	1
Co Amoxiclav	3	Topiramate	1
Ciprofloxacin	3	Furosemide	1
Metronidazole	3	Clobazam	1
Allopurinol	2	Cefazolin	1
Amoxicillin	2	Sulfasalazine	1
Cefepime	2	Rifampin	1

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Toxic Epidermal Necrolysis

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Toxic Epidermal Necrolysis Total 42

Drug Names	NO.	Drug Names	No.
Co Trimoxazole	6	Amoxicillin	1
Lamotrigine	6	Captopril	1
Phenytoin	5	Hydrochlorothiazide	1
Ceftriaxone	4	Indomethacin	1
Allopurinol	4	Sulfasalazine	1
Phenobarbital	4	Mefenamic Acid	1
Penicillin	3	Cefixim	1
Carbamazepine	2	Co Amoxiclav	1

گزارشات ارسالي به مرکز ADR
از سال 1377 تا اسفند 1389

- تعداد کل گزارشات: 25031
- تعداد گزارشات مربوط به عوارض پوستي: 8258

  درصد عوارض پوستی 32/9
- شايعترين عارضه پوستي: راش
- شايعترين دسته دارويي مسبب عارضه: ANTI-INFECTIVES
- شايعترين داروي مسبب عارضه: ونکومايسين

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شايعترين دسته هاي دارويي مسبب عوارض پوستي گزارش شده

- آنتي بيوتيكها
- داروهاي CNS
- هورمونها
- داروهای گوارشی

Anaphylaxis and Allergic Reactions

The potential morbidity and mortality associated with allergic drug reactions is great

Allergic drug reactions account for 5% to 20% of all observed adverse drug reactions

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Adverse Drug Reactions

Predictable
-Dose dependent
-Related to the pharmacologic actions of the drug

Un predictable
- Dose independent
- Related to the individual's immunologic response

Drug allergy or drug hypersensitivity is an unpredictable adverse drug reaction that is immunologically mediated

Definition of anaphylaxis

Anaphylaxis is a severe life-threatening generalized or systemic hypersensitivity reaction.

It is commonly, but not always, mediated by an allergic mechanism, usually by IgE.

Allergic (immunologic) non-IgE-mediated anaphylaxis also occurs.

Non-allergic anaphylactic reactions, formerly called anaphylactoid or pseudo-allergic reactions, may also occur.

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Primary symptoms of anaphylaxis

- **Skin**:

  flushing, itching, urticaria, angioedema

- **Gastrointestinal**:

  nausea, vomiting, bloating, cramping, diarrhea

- **Respiratory**:

  dysphonia, cough, stridor, wheezing, dyspnea, chest tightness, asphyxiation, death

- **Cardiovascular**: tachycardia, hypotension, dizziness, collapse, death

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Measures to reduce the incidence of drug-induced anaphylaxis

General measures

- obtain **detailed history** of previous adverse reactions to drugs
- **avoid drugs that cross-react** with any agents to which patient is sensitive
- administer drugs **orally rather than parenterally** when possible
- check all drugs for proper **labeling**
- **monitor patients closely** for 20 to 30 minutes after injections

Measures to reduce the incidence of anaphylaxis

- **identify causative factors**; provide specific instructions about avoidance
- teach self-injection of epinephrine and caution patients to keep it with them at all times
- repeat instructions each year

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Measures to reduce the incidence of anaphylaxis

Use preventive techniques when patients need to undergo a procedure or take an agent which places them at risk, such as:

- pretreatment
- provocative challenge *(selected patients, physician-monitored, preferably in hospital)*
- desensitization (selected patients, physician-monitored, preferably in hospital)

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Prevention of anaphylactic reactions to radiocontrast media (RCM) in adults

- Prednisolon50-100mg orally 12,7,1hours before administration RCM
- Diphenhydramine 50 mg orally/intramascularly 1hour prior to RCM
- Ephedrine 25 mg orally 1hour before RCM administration
- Another approach:
- Give oral non-sedating H1 antihistamine and H2 antihistamin at12 and1 hours before expusure.

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Factors affecting prognosis

Factor	Poor Prognosis	Good Prognosis
Onset of symptoms	Early	Late
Initiation of treatment	Late	Early
Route of exposure	Injection	Oral*
Presence of underlying disease	Yes	No

* true for drugs, not foods

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