Antibiotic Hypersensitivity Diagnosis & Management Strategies

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Disclosures

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Classification

- **Coombs and Gell classification**

- **Type I – immediate**
- **Type II - antibody-dependent**
- **Type III - immune complex**
- **Type IV - cell-mediated or delayed**

Case #1

- A 23yo male comes in after camping over the weekend. He was out in the woods and now has a rash. It is very itchy and came up after about 3d after his trip. The lesions consist of small yellowish blisters that show swelling. There are no other people who are affected in the group. What type of hypersensitivity reaction is he having?

- A: Type I
- B: Type II
- C: Type III
- D: Type IV
- E: Type V

Type I - immediate (anaphylactic)

- Type I hypersensitivity is an allergic reaction provoked by re-exposure to a specific **antigen**.
- The reaction is mediated by **IgE antibodies** and produced by the immediate release of **histamine, tryptase**, **arachidonate** and derivatives by **mast cells**.
- Exposure may be by **ingestion, inhalation, injection**, or direct contact.

Type I - immediate (anaphylactic)

- This causes an inflammatory response leading to an immediate (within seconds to minutes) reaction.
- The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock.
- Treatment usually involves **epinephrine**, **antihistamines**, and **corticosteroids**

Type II - antibody-dependent

- In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.
  - Blood is the medium
- The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (absorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen

Type II - antibody-dependent

- IgG antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation for eliminating cells presenting foreign antigens (which are usually, but not in this case, pathogens).
- As a result mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death.
- The reaction takes hours to a day.

Examples

- Autoimmune hemolytic anemia
- Pernicious anemia
- Immune thrombocytopenia
- Transfusion reactions
- Hashimoto's thyroiditis
- Graves' disease
- Myasthenia gravis
- Farmer's Lung
- Hemolytic disease of the newborn

Type III - immune complex

- In type III hypersensitivity soluble immune complexes (aggregations of antigens and IgG antibodies) form and are deposited in various tissues
  - Tissue is the medium
  - Deposition is usually in: skin, kidney and joints
- This may trigger an immune response according to the classical pathway of complement activation.
- The reaction takes hours to days to develop

Examples

- Immune complex glomerulonephritis
- Rheumatoid arthritis
- Serum sickness
- Subacute bacterial endocarditis
- Symptoms of malaria
- Systemic lupus erythematosus
- Arthus reaction

Type IV Hypersensitivity – cell mediated

- Type IV hypersensitivity is often called delayed type as the reaction takes two to three + days to develop.

- Unlike the other types, it is not antibody mediated but rather is a type of cell-mediated response.

Examples

- Contact dermatitis - poison ivy rash
- Temporal arteritis
- Symptoms of leprosy
- Symptoms of tuberculosis
- Transplant rejection

The Hypersensitivity Reactions

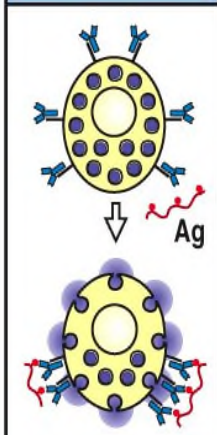
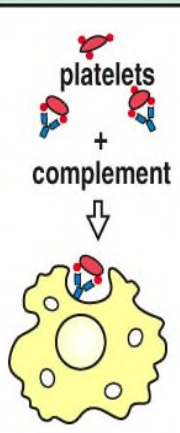
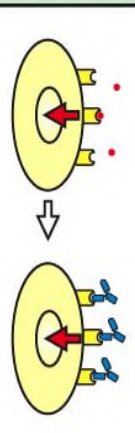
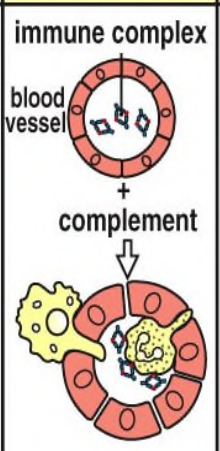
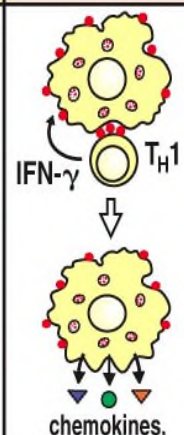
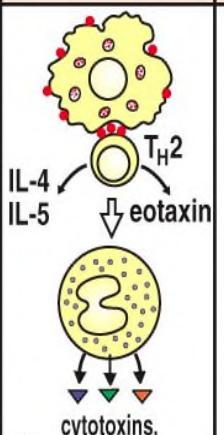
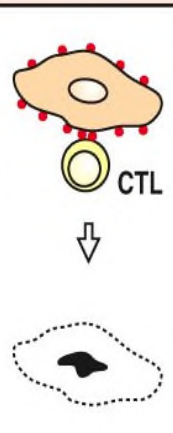
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes	Macrophage activation	IgE production, Eosinophil activation, Mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

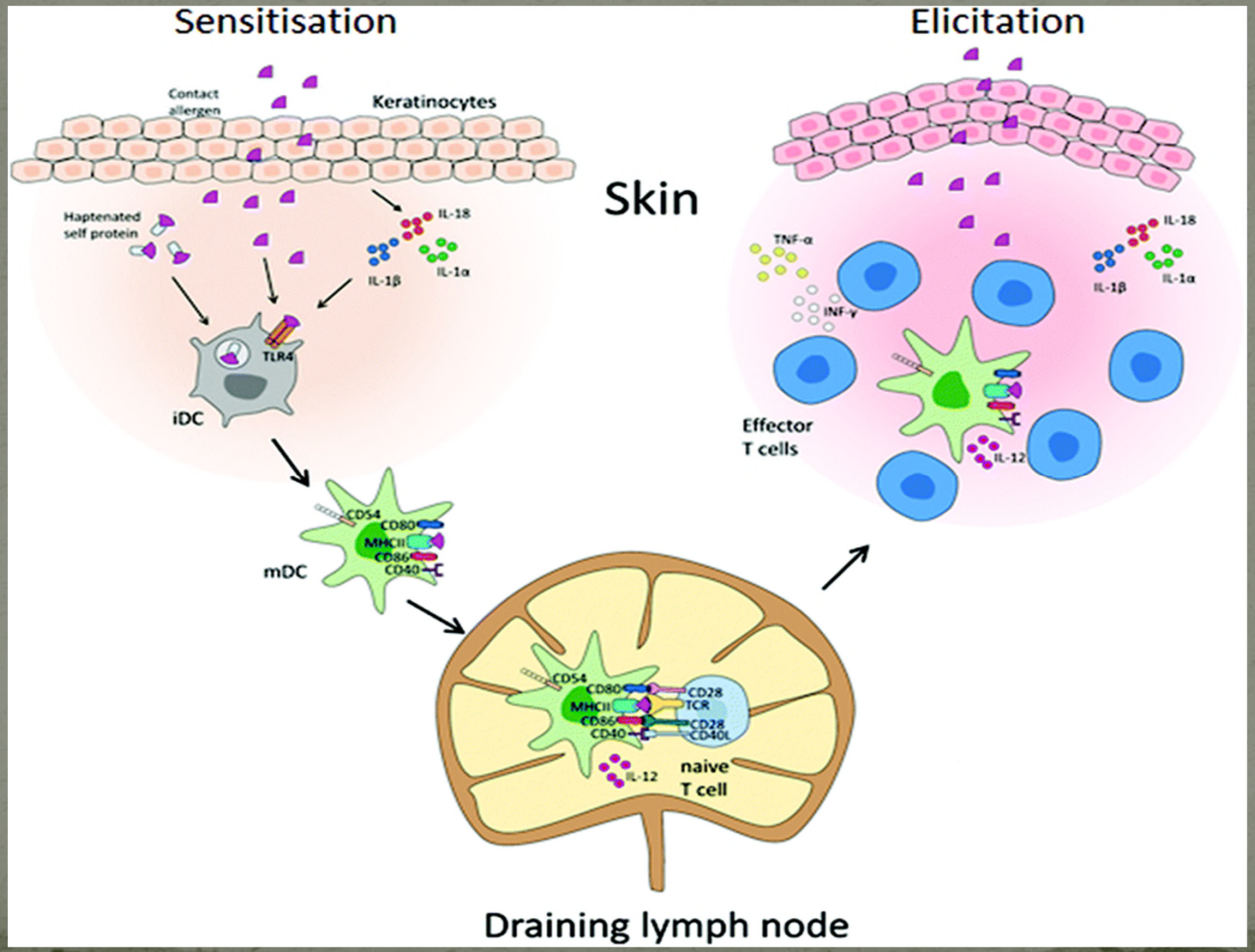
Figure 12-2 Immunobiology, 6/e. (© Garland Science 2005)

Drug Reactions

Stratification According to the Chemical Nature of the Antigen

- Hapten
  - a small separable part of an antigen that reacts specifically with an antibody but is incapable of stimulating antibody production except in combination with a carrier protein molecule
- **Direct haptenation**
  - e.g. Beta-lactam antibiotics
- **Haptenation by drug metabolites**
  - e.g. Sulfonamides
- **Complete antigens**
  - e.g. Insulin

Haptenation



Application of proteomics in the elucidation of chemical-mediated allergic contact dermatitis . Toxicology Research. Tessa Höper

Antibiotic Hypersensitivity Diagnosis & Management Strategies

- Diagnosis
  - History
  - Skin testing
  - In Vitro testing
  - Challenges

Drug Hypersensitivity - History

- **Nature of the reaction**
  - Is this an allergic reaction?
  - If so what kind?

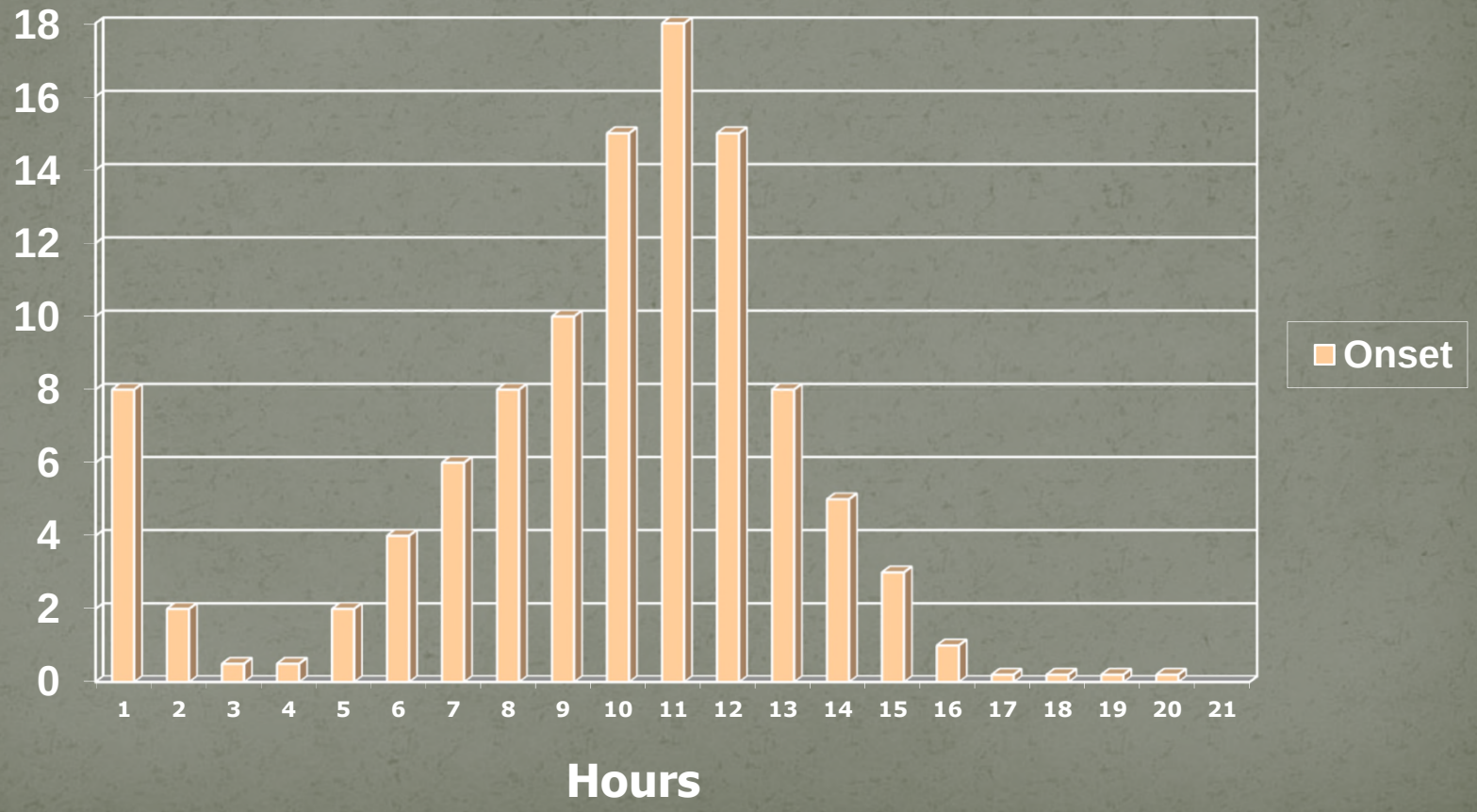
- **Temporal sequence!**
  - When did drug and other exposures occur in relation to the onset and remission of the reaction?
  - When did the itching start
  - When did the rash come up

Drug Hypersensitivity - History

- **Propensity** of the exposures to cause such a reaction.
- **Discontinuation** effect
- **Readministration** effect

Onset of Allergic Reactions

Previously Sensitized or Unsensitized



Anaphylaxis Timing

- Exposure-Response Intervals
  - Onset within 15 minutes -- 85%
  - Onset within 30-60 minutes -- 96%
  - Onset within 12 hours -- ~100%

- **Anaphylactoid reactions** are defined as those reactions that produce the same clinical picture with anaphylaxis but are not IgE mediated, occur through a direct nonimmune-mediated release of mediators from mast cells and/or basophils or result from direct complement activation.
  - "Pseudoallergic" reactions can occur after any dose:
    - Vancomycin, opiates, NSAID, IV contrast dye

Idsoe, Bull WHO 1968;38:159

Metabolic Drug Issues

- While many drug reactions are immunologic (such as with penicillins, cephalosporins, sulfonamides, quinine), others are idiosyncratic and depend on pharmacogenetics (such as with G6PD deficiency and Primaquine, or with acetylator status and Isoniazid)

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic disorder that is most common in males. G6PD deficiency mainly affects red blood cells. The most common result is hemolytic anemia.

- In G6PD deficiency, pts may not have symptoms. Symptoms happen if red blood cells are exposed to certain chemicals in food or medicine, certain bacterial or viral infections, or stress. They may include:
  - Paleness
  - Jaundice
  - Dark urine
  - Fatigue
  - Shortness of breath
  - Enlarged spleen

- Drugs to avoid:
  - Chloroquine
  - Mefloquine
  - Pamaquine.
  - Primaquine.
  - Quinidine.
  - Quinine.

Immunodiagnostic Tests

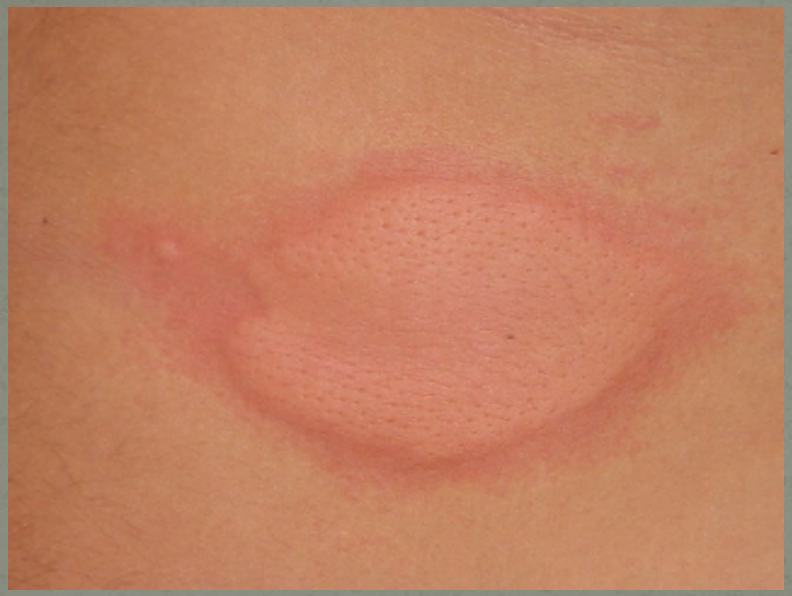
- **IgE to medications**
  - Epicutaneous & ID skin tests
  - In vitro tests for specific IgE
- **T-cells reactive with drug determinants**
  - Patch tests
  - Intradermal tests
  - In vitro tests for lymphocyte reactivity

Case # 2

- This 27 year old insulin dependent diabetic man had done well on insulin for 2 years. For the past week he has had severe generalized urticaria immediately after each of his twice daily NPH insulin injections. The urticaria would be nearly gone before his next injection.
- What type of hypersensitive is this and how would you test for this?

- A: Type I with patch testing
- B: Type III with intradermal skin testing
- C: Type IV with blood IgE testing
- D: Type I with intradermal skin testing
- E: Type V with intradermal skin testing

Urticaria



- Sharply circumscribed
- Raised
- Pruritic
- Transient lesions
- No residual abnormalities

Diagnostic Problems: Case #3

- A 32 year old man developed generalized urticaria, periodic flushing, a systemic rash, and wheezing about 1wk after a surgical procedure. He has been having itching systemically along with fatigue. He was in semi-good health but dealing with diet control DM-II. There was no hx of asthma or other lung related issues in his PMHx.

- He was having a hernia fixed and tolerated the procedure well. He and his surgeon want to know if this has something to do with the surgical procedure or if there is something else going on?

Diagnostic Problems: Case #3

- What steps should be taken?
  - Obtain the anesthesiologist record of the case for temporal verifications
  - Obtain hospital records
  - Compile a list of exposures
  - Do not forget about latex allergy

Case #3

- There was no documentation of a rash or any abnormal vital signs at the start of the surgery.
  - Records show that Iodine was used to prep the area.
  - He was given a dosage of Cefalexin just after he had anesthesia for the surgery.
  - He did have some HTN during the case and was given Hydralazine for this.
  - No latex was used.
- He did develop a rash when he was in post op but he was given Benadryl and this resolved.
- Labs:
  - CBC – WNL
  - CMP – elevated glucose, Cr and BUN
- What would you do next?
  - A: CXR
  - B: Skin culture of the wound
  - C: Monitor
  - D: Order immune labs
  - E: Treat with steroids

Case #3

- Immunological labs show:
  - ANA – Elevated
  - Antihistones – Elevated
  - SED – Elevated

- What type of hypersensitivity reaction is this man having:
  - A: Type I
  - B: Type II
  - C: Type III
  - D: Type IV
  - E: Type V

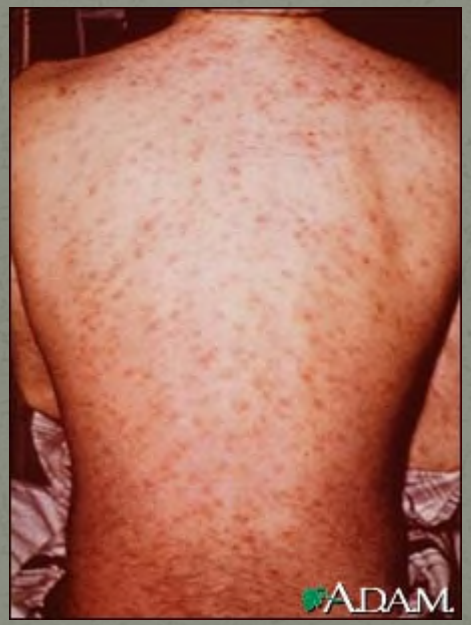
Drug-Induced Glomerular Disease: Immune-Mediated Injury. Clin J Am Soc Nephrol. 2015 Jul 7; 10(7): 1300–1310.

Beta-Lactam Drugs

- Maculopapular rashes
- Negative skin and in vitro tests for specific IgE
- Positive patch and ID skin tests read at 48 and 72 hours
- Positive oral challenges in patch test positives, not in negative controls

Patriarca et. al. Ann Allergy Asthma Immunol 1999;83:257-266.

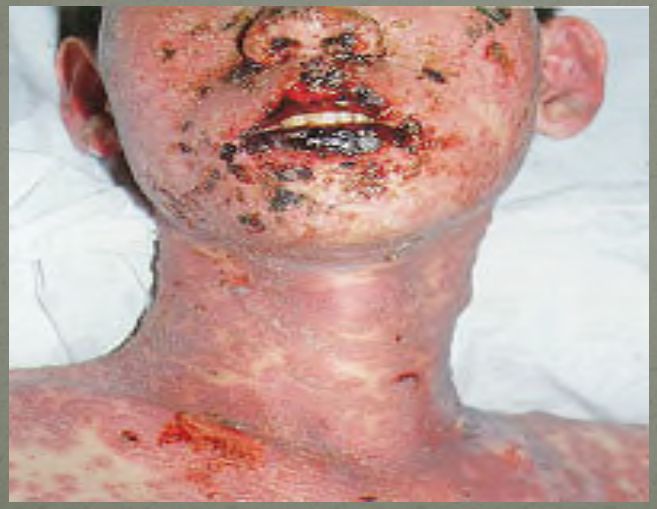
Maculopapular rashes



- Relatively non-pruritic
- Resolve without residual damage
- Benign
- Drug associated may be specific lymphocyte mediated

Case #4

- 26 year-old man admitted to the hospital with cc of having a very bad rash after he started to take some Carbamazepine for his seizure disorder.



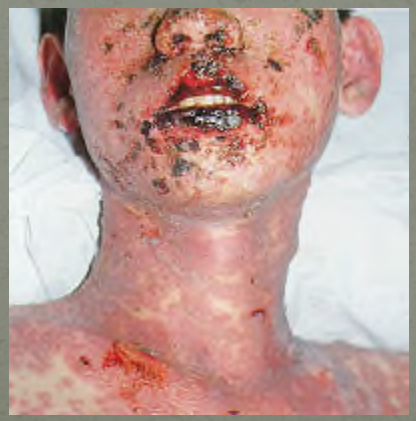
- What type of reaction is he having and how would you treat this:

- A: Type III – but change to dexamethasone
- B: Type IV - IVIg
- C: Type III - Cyclosporin
- D: Type IV - Cyclosporin
- E: None of the above

What if EM, S-J, or TEN Occur?

Cause	No. (%)
Drug-related	43 (52.4)
Single drug	
Anticonvulsant	12 (14.6)
Carbamazepine	7 (8.5)
Phenytoin	2 (2.4)
Valporic acid	2 (2.4)
Phenobarbital	1 (1.2)
Antibiotics	9 (11)
Cephalosporin	4 (4.9)
Penicillin	2 (2.4)
Levofloxacin	1 (1.2)
TMP-SMZ	1 (1.2)
Doxycyline	1 (1.2)
NSAID	5 (6.1)
Herb	5 (6.1)
Allopurinol	2 (2.4)
Antipsychotic	1 (1.2)
Famciclovir	1 (1.2)
L-cysteine	1 (1.2)
Hair dye	1 (1.2)
Multiple drugs	
Diazepam and dantrolene sodium	1 (1.2)
Nimesulide and lansoprazole	1 (1.2)
Cefadroxil and naproxen	3 (3.7)
Hydantoin, meloxicam, and levofloxacin	1 (1.2)
Non-drug-related	39 (47.6)

- Type IV reaction that involves activated T cells in lesions
- Antigen specific T cells in blood
- Apoptosis in lesions
- A T-cell mediated process
- Responses to medications



What if EM, S-J, or TEN Occur?

- Cyclosporine or other agents for T-lymphocyte mediated reactions
  - Glucocorticoids are logical, but weak
  - Cyclosporine 5 mg/kg/day (15 mg/kg full immunosuppressive dose)
- Prograf and others as alternatives
- IVIg – Not effective in some reported trials

Antibiotic Hypersensitivity Diagnosis & Management Strategies

- Management
  - Avoidance

- Desentization
  - Referral to allergy can help establish what drugs could be causing the issue and if there is a way to overcome the allergy
    - Treating through false reactions
    - Acute desensitization
    - Slow desensitization
    - Treatment of reactions
  - Desentization is a short term fix for a problem. The allergy will re-occur s/p discontinuation of the drug in question.

Conclusions

- Drug allergy diagnosis is very difficult
- History is key when determining what drugs are players and eventually what to test.
- Establish what type of hypersensitivity the reaction is in order to determine what course of action to treat.
- Consider desentization if applicable to the case.