Hypersensitivity Reactions of the Ocular Surface
Firstly: What is a Hypersensitivity Reaction of the Ocular Surface?
Firstly: What is a Hypersensitivity Reaction? of the Ocular Surface?
An exaggerated version of a normal immune response—ie, too much of a good thing
How many *Hypersensitivity Reactions of the Ocular Surface* are there?
How many *Hypersensitivity Reactions of the Ocular Surface* are there?

- **Type I**
- **Type II**
- **Type III**
- **Type IV**
How many Hypersensitivity Reactions of the Ocular Surface are there?

Type I  Type II  Type III  Type IV

Four? But I seem to recall from med school that there are five hypersensitivity reactions. What gives?
How many *Hypersensitivity Reactions of the Ocular Surface* are there?

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Four? But I seem to recall from med school that there are *five* hypersensitivity reactions. What gives? There is a fifth, but it plays no role regarding the ocular surface.
Before proceeding further, it should be noted that the conceptualization of 4 (or 5) distinct hypersensitivity reactions is considered **outdated** by modern immunologists. In truth, most clinical conditions represent a blend of the proposed hypersensitivity mechanisms. That said, this framework for categorizing hypersensitivity reactions persists in the literature, and thus familiarity with it remains an obligation of ophthos-in-training.
Hypersensitivity Reactions of the Ocular Surface

Type I

Type II

Type III

Type IV

Type I reactions involve...
Type II reactions involve...
Type III reactions involve...
Type IV reactions involve...
**Hypersensitivity Reactions of the Ocular Surface**

**Anaphylaxis**

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**Type I reactions involve...Anaphylaxis**

**Type II reactions involve...**

**Type III reactions involve...**

**Type IV reactions involve...**
### Hypersensitivity Reactions of the Ocular Surface

**Anaphylaxis**

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**Briefly, how does an anaphylactic reaction proceed?**
Hypersensitivity Reactions of the Ocular Surface

Anaphylaxis

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Briefly, how does an anaphylactic reaction proceed?
The binding of one word, + its abb. to Ig... receptors on cell type causes the cells to one word, with the subsequent release of one word, and other pre-formed inflammatory mediators
**Hypersensitivity Reactions of the Ocular Surface**

**Anaphylaxis**

**Type I**

*Type I reactions involve*...

Anaphylaxis

**Type II**

*Type II reactions involve*...

**Type III**

*Type III reactions involve*...

**Type IV**

*Type IV reactions involve*...

**Briefly, how does an anaphylactic reaction proceed?**

The binding of antigen (Ag) to IgE receptors on mast cells causes the cells to degranulate, with the subsequent release of histamine and other pre-formed inflammatory mediators.
Hypersensitivity Reactions of the Ocular Surface

**Anaphylaxis**

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**Type I reactions involve...** Anaphylaxis
**Type II reactions involve...**
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**Type IV reactions involve...**

Briefly, how does an anaphylactic reaction proceed?
The binding of **antigen (Ag)** to **IgE** receptors on **mast cells**
causes the cells to **degranulate**, with the subsequent release of
**histamine** and other pre-formed inflammatory mediators

**Sounds fast. How long does it take to become clinically apparent?**
Type I reactions involve…Anaphylaxis
Type II reactions involve…
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Briefly, how does an anaphylactic reaction proceed?
The binding of antigen (Ag) to IgE receptors on mast cells causes the cells to degranulate, with the subsequent release of histamine and other pre-formed inflammatory mediators.

Sounds fast. How long does it take to become clinically apparent?
Only minutes, which is why this reaction is often referred to as immediate hypersensitivity.
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*Type I reactions involve... Anaphylaxis*
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*Type I reactions involve... Anaphylaxis*
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*Is the antibody (Ab) involved in Type II reactions IgE, as it is in Type I?*
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**Type I reactions involve…** Anaphylaxis

**Type II reactions involve…** Cytotoxic antibodies

**Type III reactions involve…**

**Type IV reactions involve…**

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*Is the antibody (Ab) involved in Type II reactions IgE, as it is in Type I?*

No, it is IgG and/or IgM
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- **Type I reactions involve…** Anaphylaxis
- **Type II reactions involve…** Cytotoxic antibodies
- **Type III reactions involve…** Immune-complex reactions
- **Type IV reactions involve…** Immune-complex reactions

*Is the antibody (Ab) involved in Type II reactions IgE, as it is in Type I?*

No, it is IgG and/or IgM

*How does a Type II reaction proceed?*
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*Is the antibody (Ab) involved in Type II reactions IgE, as it is in Type I?*
No, it is IgG and/or IgM

*How does a Type II reaction proceed?*
Antibodies bind to antigens located on cell membranes. These cell-membrane bound Ag-Ab complexes prompt complement-system attacks on the cell.
## Hypersensitivity Reactions of the Ocular Surface

### Type I
- **Anaphylaxis**

### Type II
- **Cytotoxic Ab**

### Type III
- **Immune-complex reactions**

### Type IV
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**Type I reactions involve...** Anaphylaxis  
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**Type I reactions involve...** Anaphylaxis

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Is the antibody involved in Type III IgE à la Type I, or IgG and IgM as in Type II?
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*Is the antibody involved in Type III IgE a la Type I, or IgG and IgM as in Type II? IgG and/or IgM*
Hypersensitivity Reactions of the Ocular Surface

**Type I**
- Anaphylaxis

**Type II**
- Cytotoxic antibodies

**Type III**
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*Is the antibody involved in Type III IgE a la Type I, or IgG and IgM as in Type II? IgG and/or IgM*

*How does a Type III reaction proceed?*
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**Type I reactions involve…** Anaphylaxis  
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**Is the antibody involved in Type III IgE a la Type I, or IgG and IgM as in Type II?**  
IgG and/or IgM  

**How does a Type III reaction proceed?**  
Antibodies bind to antigens circulating in the bloodstream. The resulting Ab-Ag complexes get deposited somewhere (often on the lining of a blood vessel). Once ensconced in tissue, the Ab-Ag complexes precipitate attacks on the tissue by PMNs.
Hypersensitivity Reactions of the Ocular Surface

Type I reactions involve...
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Is the antibody involved in Type III IgE a la Type I, or IgG and IgM as in Type II? IgG and/or IgM

How does a Type III reaction proceed?
Antibodies bind to antigens circulating in the bloodstream. The resulting Ab-Ag complexes get deposited somewhere (often on the lining of a blood vessel). Once ensconced in tissue, the Ab-Ag complexes precipitate attacks on the tissue by PMNs.

Types II and III are easily confused with one another. Note the key differences:
--In Type II, Ab attach to cell-bound Ag, whereas in Type III they attach to circulating Ag
--In Type II, the damage is caused by complement, whereas in Type III it is caused by PMNs
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Hypersensitivity Reactions of the Ocular Surface

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‘Cell-mediated reaction’...Which sort of immune cell is doing the mediating?
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‘Cell-mediated reaction’...Which sort of immune cell is doing the mediating?
T-helper cells
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‘Cell-mediated reaction’…Which sort of immune cell is doing the mediating?
T-helper cells

In what way are T-helper cells mediating the reaction?
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‘Cell-mediated reaction’...Which sort of immune cell is doing the mediating?

T-helper cells

In what way are T-helper cells mediating the reaction?

In Type IV reactions, T-helpers interact with antigens, thereby becoming activated. Once activated, the T-helpers release chemotactic factors that recruit and activate macrophages.
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‘Cell-mediated reaction’…Which sort of immune cell is doing the mediating? T-helper cells

In what way are T-helper cells mediating the reaction?
In Type IV reactions, T-helpers interact with antigens, thereby becoming activated. Once activated, the T-helpers release chemotactic factors that recruit and activate macrophages.

That’s a convoluted process. How long does it take to become clinically apparent?
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‘Cell-mediated reaction’…Which sort of immune cell is doing the mediating? T-helper cells

*In what way are T-helper cells mediating the reaction?*
In Type IV reactions, T-helpers interact with antigens, thereby becoming activated. Once activated, the T-helpers release chemotactic factors that recruit and activate macrophages.

*That’s a convoluted process. How long does it take to become clinically apparent?* 24-72 hours, which is why this reaction is often referred to as *delayed hypersensitivity.*
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**Type I reactions involve...** Anaphylaxis
**Type II reactions involve...** Cytotoxic antibodies
**Type III reactions involve...** Immune-complex reactions
**Type IV reactions involve...** Delayed hypersensitivity

‘Cell-mediated reaction’... Which sort of immune cell is doing the mediating? T-helper cells

In what way are T-helper cells mediating the reaction? In Type IV reactions, T-helpers interact with antigens, thereby becoming activated. Once activated, the T-helpers release chemotactic factors that recruit and activate macrophages.

That’s a convoluted process. How long does it take to become clinically apparent? 24-72 hours, which is why this reaction is often referred to as delayed hypersensitivity.

Note that if you remember Type IV as ‘delayed hypersensitivity’...
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- **Type I** reactions involve... **Anaphylaxis**
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‘Cell-mediated reaction’...Which sort of immune cell is doing the mediating? T-helper cells

In what way are T-helper cells mediating the reaction?

In Type IV reactions, T-helpers interact with antigens, thereby becoming activated. Once activated, the T-helpers release chemotactic factors that recruit and activate macrophages.

That’s a convoluted process. How long does it take to become clinically apparent? 24-72 hours, which is why this reaction is often referred to as **delayed hypersensitivity**.

**Note that if you remember Type IV as ‘delayed hypersensitivity’...**

**the four forms can be remembered with the mnemonic ACID**
Hypersensitivity Reactions of the Ocular Surface

Divvy ‘em up

Anaphylaxis

Type I

Cytotoxic Ab

Type II

Immune-complex reactions

Type III

Cell-mediated reactions

Type IV

Topical anesthetics

Neomycin

Anaphylaxis

IgE

Histamine release

Cicatricial pemphigoid

Mast-cell degranulation

Vasculitis

Atropine

Contact dermatitis

Chemosis

PK rejection

SLE

Red excematous periorbital skin

Peripheral ulcerative keratitis

Involves complement

Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface

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Hypersensitivity Reactions of the Ocular Surface

Divvy 'em up

- **Type I**
  - Topical anesthetics

- **Type II**
  - Cytotoxic Ab

- **Type III**
  - Immune-complex reactions

- **Type IV**
  - Cell-mediated reactions
    - Neomycin

**Anaphylaxis**
- IgE
- Histamine release
- Cicatricial pemphigoid
- Mast-cell degranulation
- Vasculitis
- Atropine
- Contact dermatitis
- Chemosis
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**Histamine release**
- Cicatricial pemphigoid
- Mast-cell degranulation
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**Neomycin**
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**Divvy ‘em up**

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**Cicatricial pemphigoid**
- Mast-cell degranulation
- Vasculitis
- Atropine
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<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Topical anesthetics</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>IgE</td>
</tr>
<tr>
<td></td>
<td>Histamine release</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>Cytotoxic Ab</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>Immune-complex reactions</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>Cell-mediated reactions</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
</tr>
</tbody>
</table>

- **Type I** (Anaphylaxis)
  - Topical anesthetics
  - Anaphylaxis
  - IgE
  - Histamine release

- **Type II** (Cytotoxic Ab)

- **Type III** (Immune-complex reactions)

- **Type IV** (Cell-mediated reactions)

- **Cicatricial pemphigoid**
  - Mast-cell degranulation
  - Vasculitis
  - Atropine
  - Contact dermatitis
  - Chemosis
  - PK rejection
  - SLE

- Red excematous periorbital skin
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface

Divvy ‘em up

Type I
- Topical anesthetics
- Anaphylaxis
- Histamine release

Type II
- Cytotoxic
- Cytotoxic Abs

Type III
- Immune-complex reactions

Type IV
- Cell-mediated reactions
- Neomycin

Ocular Cicatricial Pemphigoid (OCP) is now referred to by what name in the BCSC Cornea book?

Atropine
Contact dermatitis
Chemosis
PK rejection
SLE
Red excematous periorbital skin
Peripheral ulcerative keratitis
Involves complement
Phlyctenulosis
**Hypersensitivity Reactions of the Ocular Surface**

*Divvy ‘em up*

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-complex</td>
<td>Cytotoxic Ab</td>
<td>Cytotoxic</td>
<td>Cell-mediated</td>
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<td>reactions</td>
<td>reactions</td>
<td>reactions</td>
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<tr>
<td>Topical anesthetics</td>
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<td>Neomycin</td>
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<tr>
<td>Anaphylaxis</td>
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</tr>
<tr>
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<td>Histamine release</td>
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</tr>
</tbody>
</table>

**Ocular Cicatricial Pemphigoid (OCP)** is now referred to by what name in the BCSC Cornea book?

**Mucous membrane pemphigoid (MMP)**

- Atropine
- Contact dermatitis
- Chemosis
- PK rejection
- SLE
- Red exccematous periorbital skin
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface

Divvy 'em up

<table>
<thead>
<tr>
<th>Anaphylaxis</th>
<th>Cytotoxic Ab</th>
<th>Immune-complex reactions</th>
<th>Cell-mediated reactions</th>
</tr>
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<tbody>
<tr>
<td><strong>Type I</strong></td>
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<td><strong>Type III</strong></td>
<td><strong>Type IV</strong></td>
</tr>
<tr>
<td>Topical anesthetics</td>
<td></td>
<td></td>
<td>Neomycin</td>
</tr>
</tbody>
</table>

Anaphylaxis
- IgE
- Histamine release

Cicatricial pemphigoid

**Mast-cell degranulation**
- Vasculitis
- Atropine
- Contact dermatitis
- Chemosis
- PK rejection
- SLE
- Red excematous periorbital skin
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface

Divvy 'em up

Anaphylaxis

Cytotoxic Ab

Immune-complex reactions

Cell-mediated reactions

Type I
Topical anesthetics

Type II
Anaphylaxis
IgE
Histamine release

Type III
Cicatricial pemphigoid

Type IV
Neomycin

Vasculitis

Atropine
Contact dermatitis
Chemosis
PK rejection
SLE
Red excematous periorbital skin
Peripheral ulcerative keratitis
Involves complement
Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface

**Divvy 'em up**

- **Anaphylaxis**
  - Type I
    - Topical anesthetics
  - Type II
    - Anaphylaxis
    - IgE
    - Histamine release
  - Type III
    - Cicatricial pemphigoid
    - Mast-cell degranulation
- **Cytotoxic Ab**
  - Type II
  - Type III
  - Type IV
- **Immune-complex reactions**
  - Neomycin
- **Cell-mediated reactions**
  - Neomycin

- **Atropine**
  - Contact dermatitis
  - Chemosis
  - PK rejection
  - SLE
  - Red excematous periorbital skin
  - Peripheral ulcerative keratitis
  - Involves complement
  - Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface
Divvy ‘em up

Anaphylaxis

Type I
Topical anesthetics
Anaphylaxis
IgE
Histamine release

Cytotoxic Ab

Type II

Immune-complex reactions

Type III
Cicatricial pemphigoid
Mast-cell degranulation

Cell-mediated reactions

Type IV

Neomycin

Atropine

Contact dermatitis

Chemosis
PK rejection
SLE
Red excematos periorbital skin
Peripheral ulcerative keratitis
Involves complement
Phlyctenulosis
**Hypersensitivity Reactions of the Ocular Surface**

*Divvy 'em up*

- **Type I**
  - Anaphylaxis
  - Topical anesthetics
  - Anaphylaxis
  - IgE
  - Histamine release
  - Mast-cell degranulation

- **Type II**
  - Cytotoxic Ab
  - Topical anesthetics
  - Cytotoxic Ab
  - IgE
  - Histamine release

- **Type III**
  - Immune-complex reactions
  - Cicatricial pemphigoid
  - Mast-cell degranulation

- **Type IV**
  - Cell-mediated reactions
  - Neomycin
  - Atropine
  - Contact dermatitis

**Chemosis**
- PK rejection
- SLE
- Red excematous periorbital skin
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis
**Hypersensitivity Reactions of the Ocular Surface**  

**Divvy ‘em up**

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Anaphylaxis</td>
<td>Topical anesthetics, Neomycin</td>
</tr>
<tr>
<td>Type II</td>
<td>Cytotoxic Ab</td>
<td>Immune-complex reactions</td>
</tr>
<tr>
<td>Type III</td>
<td>Cicatricial pemphigoid</td>
<td>Mast-cell degranulation, IgE, Histamine release</td>
</tr>
<tr>
<td>Type IV</td>
<td>Cytophagic</td>
<td>Neomycin, Contact dermatitis</td>
</tr>
</tbody>
</table>

**PK rejection** *(PK = Penetrating keratoplasty; ie a corneal transplant)*

- SLE
- Red exematous periorbital skin
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis
Hypersensitivity Reactions of the Ocular Surface

Divvy ‘em up

**Type I**
Topical anesthetics

**Type II**
- Anaphylaxis
- Cytotoxic Ab
- Histamine release
- Chemosis
- PK rejection

**Type III**
- Neomycin
- Cicatricial pemphigoid
- Mast-cell degranulation
- SLE
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis

**Type IV**
- Atropine
- Contact dermatitis
- PK rejection
Hypersensitivity Reactions of the Ocular Surface

Divvy 'em up

Type I
- Topical anesthetics
  - Neomycin
- Anaphylaxis
  - Histamine release
  - Mast-cell degranulation
- Cytotoxic Ab
- Immune-complex reactions
  - Cicatricial pemphigoid
- Cell-mediated reactions
  - Atropine
  - Contact dermatitis
  - PK rejection
  - SLE
  - Peripheral ulcerative keratitis
  - Involves complement
  - Phlyctenulosis

Type II
- Type II
- Type III
- Type IV
  - Red excematous periorbital skin

Firstly: How many Hypersensitivity Reactions of the Ocular Surface are there? Divvy 'em up

- Immune-complex reactions
- Cell-mediated reactions

- Anaphylaxis
- IgE
- Histamine release
- Mast-cell degranulation
- Chemosis

- Vasculitis
- PK rejection
- Contact dermatitis
- Atropine
- SLE
- Peripheral ulcerative keratitis
- Involves complement
- Phlyctenulosis
**Hypersensitivity Reactions of the Ocular Surface**  
*Divvy ‘em up*

- **Type I**  
  - Topical anesthetics  
  - Anaphylaxis  
  - IgE  
  - Histamine release  
  - Mast-cell degranulation  
  - Chemosis

- **Type II**  
  - Cytotoxic Ab  
  - Cicatricial pemphigoid  
  - Peripheral ulcerative keratitis  
  - Phlyctenulosis

- **Type III**  
  - Immune-complex reactions  
  - Vasculitis  
  - SLE

- **Type IV**  
  - Cell-mediated reactions  
  - Neomycin  
  - Atropine  
  - Contact dermatitis  
  - PK rejection  
  - Red excematous periorbital skin

Firstly: How many Hypersensitivity Reactions of the Ocular Surface are there?  
Divvy ‘em up
Hypersensitivity Reactions of the Ocular Surface

Divvy 'em up

Type I
- Topical anesthetics
  - Neomycin
  - Anaphylaxis
  - Cytotoxic Ab
  - Histamine release
  - Cicatricial pemphigoid
  - Mast-cell degranulation

Type II
- Topical anesthetics

Type III
- Immune-complex reactions
  - IgE
  - SLE
  - Peripheral ulcerative keratitis

Type IV
- Cell-mediated reactions
  - Atropine
  - Contact dermatitis
  - PK rejection
  - Neomycin
  - Red excematous periorbital skin

Firstly: How many Hypersensitivity Reactions of the Ocular Surface are there?

Divvy 'em up

Immune-complex reactions

Cell-mediated reactions

Vasculitis

SLE

Peripheral ulcerative keratitis

Involves complement

Phlyctenulosis

Red excematous periorbital skin

PK rejection

Contact dermatitis

Atropine

Neomycin

Cicatricial pemphigoid

Histamine release

Mast-cell degranulation

Topical anesthetics

Anaphylaxis

IgE

Peripheral ulcerative keratitis

Involves complement

Phlyctenulosis

Red excematous periorbital skin

PK rejection

Contact dermatitis

Atropine

Neomycin

Cicatricial pemphigoid

Histamine release

Mast-cell degranulation

Topical anesthetics

Anaphylaxis

IgE
Hypersensitivity Reactions of the Ocular Surface

Divvy ‘em up

Anaphylaxis

Type I
Topical anesthetics
Anaphylaxis
IgE
Histamine release
Mast-cell degranulation
Chemosis

Cytotoxic Ab

Type II

Immune-complex reactions

Type III

Cell-mediated reactions

Type IV
Neomycin

Atropine
Contact dermatitis
PK rejection
SLE
Red exccematous periorbital skin
Peripheral ulcerative keratitis
Phlyctenulosis

Involves complement

Involves complement
**Hypersensitivity Reactions of the Ocular Surface**

**Divvy ‘em up**

**Anaphylaxis**  
*Type I*
- Topical anesthetics
- Anaphylaxis
- IgE
- Histamine release

**Cytotoxic Ab**  
*Type II*
- Chemosis

**Immune-complex reactions**  
*Type III*
- Cicatricial pemphigoid
- Mast-cell degranulation
- Involves complement

**Cell-mediated reactions**  
*Type IV*
- Neomycin
- Atropine
- Contact dermatitis
- PK rejection
- SLE
- Red excematous periorbital skin
- Peripheral ulcerative keratitis
- Phlyctenulosis

Firstly: How many hypersensitivity reactions of the ocular surface are there?

Divvy ‘em up

- Immune-complex reactions
- Anaphylaxis
- Cytotoxic Ab
- Cell-mediated reactions