Hypersensitivity Disorders Caused by Immune Responses

The following questions are addressed:

- What are the mechanisms of different types of hypersensitivity reactions?
- What are the major clinical and pathologic features of diseases caused by these reactions, and what principles underlie treatment of such diseases?

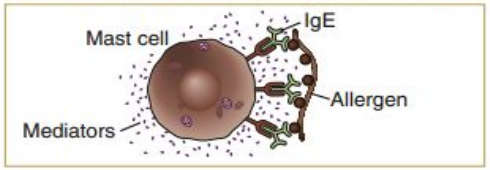
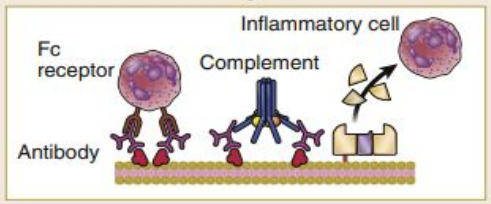
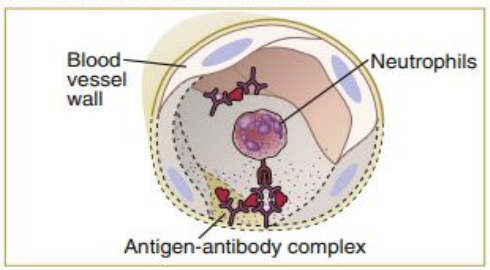
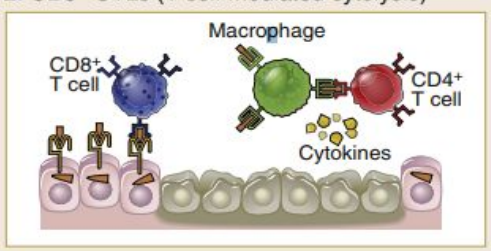
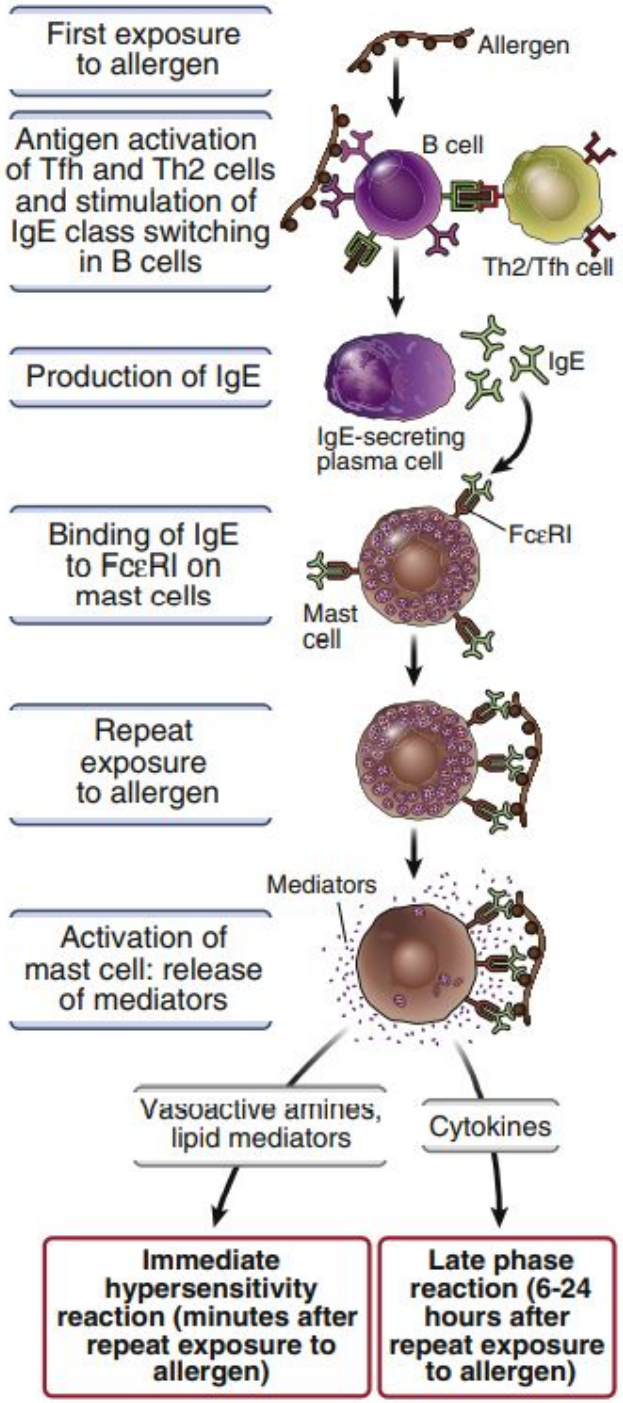
Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	Th2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils, lymphocytes)
Antibody-mediated (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function (e.g., hormone or neurotransmitter receptor signaling)
Immune complex-mediated (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes, and tissue damage secondary to impaired blood flow
T cell-mediated (Type IV)	1. $CD4^+$ T cells (cytokine-mediated inflammation) 2. $CD8^+$ CTLs (T cell-mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

FIGURE 11-1 Types of hypersensitivity reactions. In the four major types of hypersensitivity reactions,



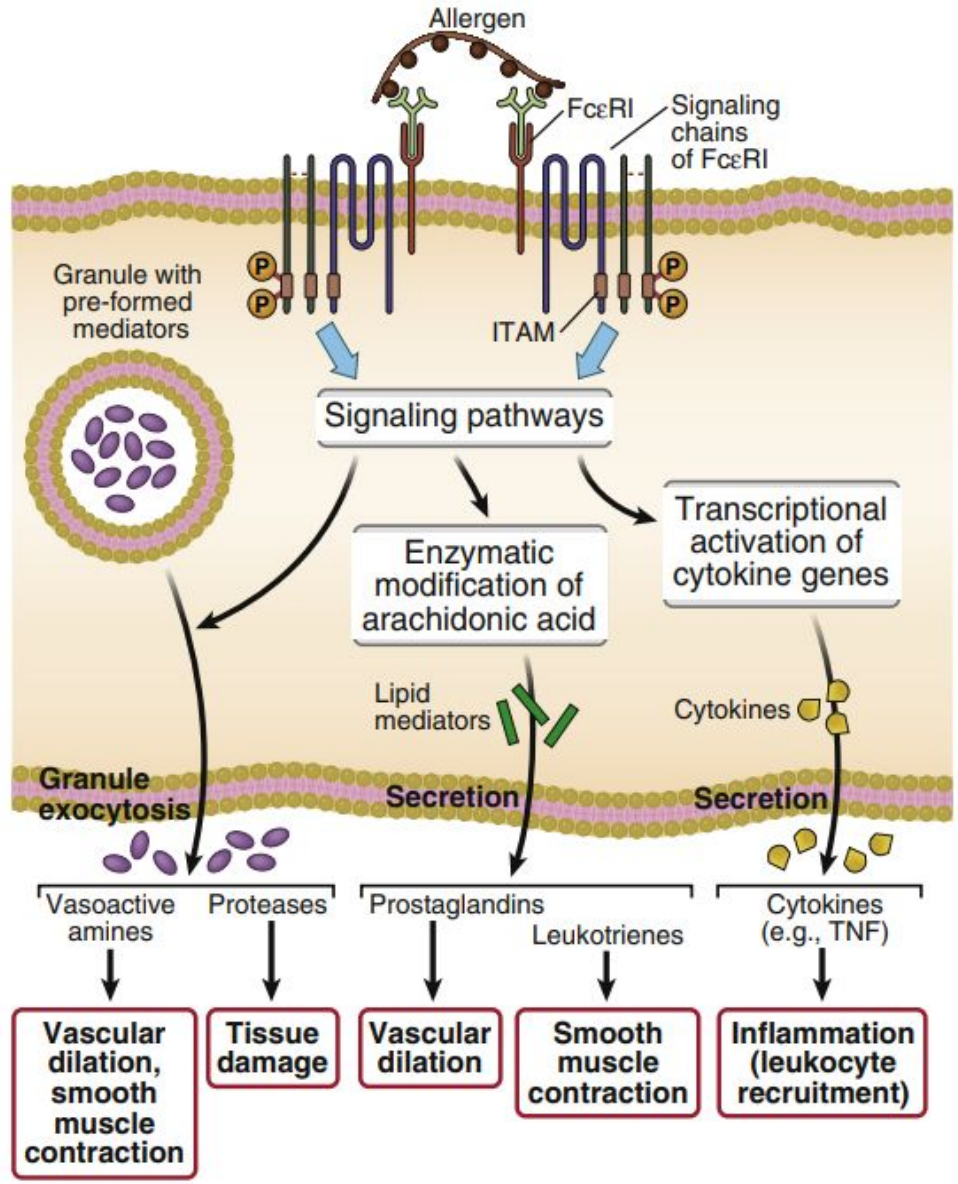


FIGURE 11-4 Production and actions of mast cell mediators. Cross-linking of immunoglobulin E (IgE) on a mast cell by an allergen stimulates phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) in the signaling chains of the IgE Fc receptor (FcεRI), which then initiates multiple signaling pathways. These signaling pathways stimulate the release of mast cell granule contents (amines, proteases), the synthesis of arachidonic acid metabolites (prostaglandins, leukotrienes), and the synthesis of various cytokines. *TNF*, Tumor necrosis factor.

Clinical syndrome	Clinical and pathological manifestations
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury caused by late-phase reaction
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilation; airway obstruction due to bronchoconstriction and laryngeal edema

FIGURE 11-5 Clinical manifestations of immediate hypersensitivity reactions. Immediate hypersensitivity may be manifested in many other ways, as in development of skin lesions (e.g., urticaria, eczema).

Syndrome	Therapy	Mechanism of action
Anaphylaxis	Epinephrine	Causes vascular smooth muscle cell contraction, increases cardiac output (to counter shock), and inhibits bronchial smooth muscle cell contraction
Bronchial asthma	Corticosteroids	Reduce inflammation
	Leukotriene antagonists	Relax bronchial smooth muscle and reduce inflammation
	Phosphodiesterase inhibitors	Relax bronchial smooth muscles
Various allergic diseases	Desensitization (repeated administration of low doses of allergens)	Unknown; may inhibit IgE production and increase production of other Ig isotypes; may induce T cell tolerance
	Anti-IgE antibody	Neutralizes and eliminates IgE
	Antihistamines	Block actions of histamine on vessels and smooth muscles
	Cromolyn	Inhibits mast cell degranulation

FIGURE 11-6 Treatment of immediate hypersensitivity reactions. The figure summarizes the principal mechanisms of action of the various drugs used to treat allergic disorders. *Ig,* Immunoglobulin.

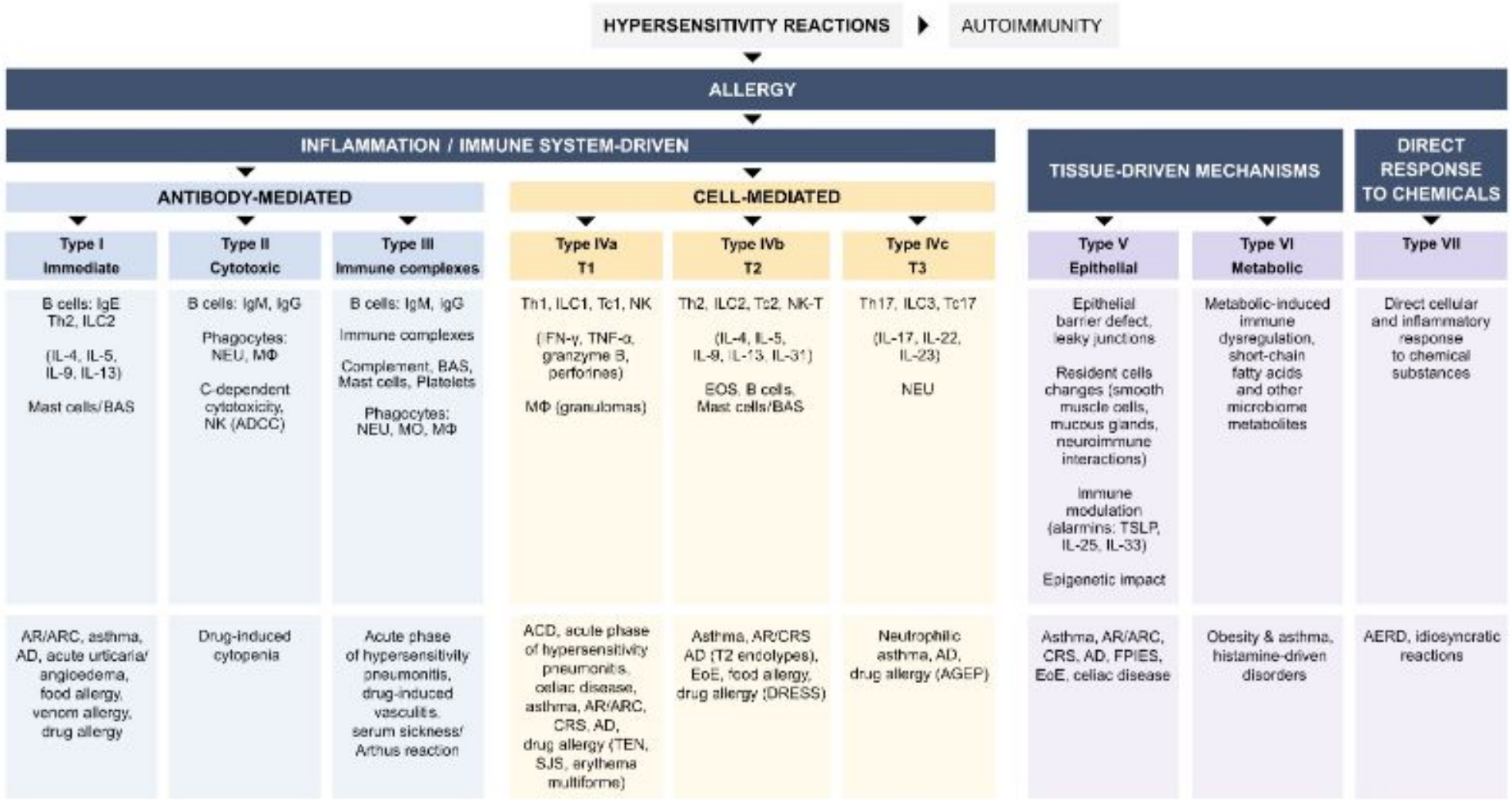


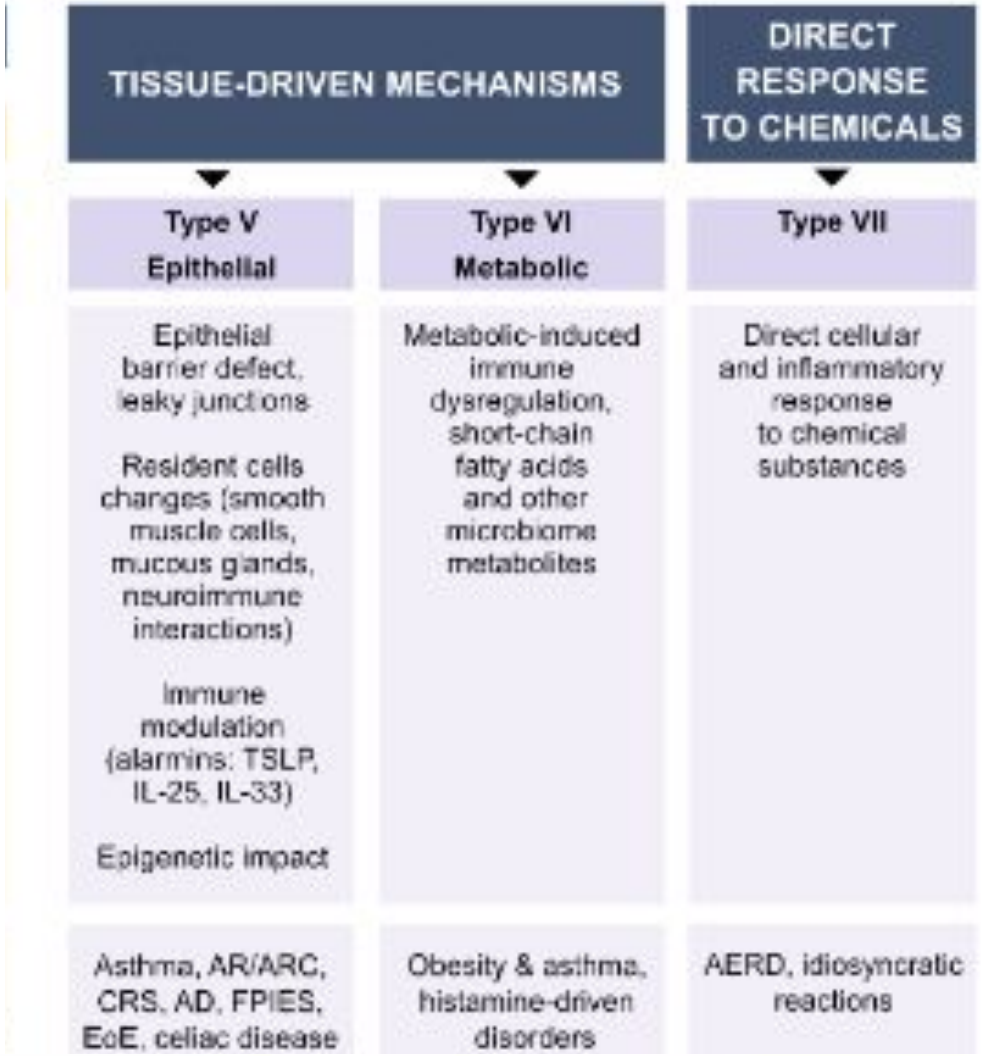
FIGURE 1 New nomenclature of allergic diseases. Hypersensitivity refers to an undesirable, uncomfortable or damaging response that arises from a tissue cell dysfunction or immune system overreaction. Allergy is an abnormal or exaggerated reaction to exogenous stimuli which involves various types of hypersensitivity reactions engaging antibodies, immune cell-mediated, tissue-driven or metabolic mechanisms resulting in the development of respiratory, skin, eye, gastrointestinal and other symptoms, including anaphylaxis. ACD, allergic contact dermatitis; AD, atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin-exacerbated respiratory diseases; AGEP, acute generalized exanthematous pustulosis; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; B, B lymphocytes; BAS, basophil; CRS, chronic rhinosinusitis; DRESS, severe drug reaction with eosinophilia and systemic symptoms; EoE, eosinophilic oesophagitis; EOS, eosinophil; FPIES, food protein-induced enterocolitis syndrome; IFN-γ, interferon-gamma; Ig (E, G, M), immunoglobulin (type E, G, M); IL, interleukin; ILC1/2/3, innate lymphoid cells type 1/2/3; MO, monocyte; Mφ, macrophage; NEU, neutrophils; NK, natural killer cell; NK-T, natural killer T cell; SJS, Stevens-Johnson syndrome; T1/T2/T3, type 1/2/3 immune response; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Th, T helper lymphocytes; TLSP, thymic stromal lymphopoietin; TNF-α, tumour necrosis factor-alpha.

ANTIBODY-MEDIATED

Type I Immediate	Type II Cytotoxic	Type III Immune complexes
B cells: IgE Th2, ILC2 (IL-4, IL-5, IL-9, IL-13) Mast cells/BAS	B cells: IgM, IgG Phagocytes: NEU, MΦ C-dependent cytotoxicity, NK (ADCC)	B cells: IgM, IgG Immune complexes Complement, BAS, Mast cells, Platelets Phagocytes: NEU, MO, MΦ
AR/ARC, asthma, AD, acute urticaria/ angioedema, food allergy, venom allergy, drug allergy	Drug-induced cytopenia	Acute phase of hypersensitivity pneumonitis, drug-induced vasculitis, serum sickness/ Arthus reaction

CELL-MEDIATED

Type IVa T1	Type IVb T2	Type IVc T3
Th1, ILC1, Tc1, NK (IFN-γ, TNF-α, granzyme B, perforines) MΦ (granulomas)	Th2, ILC2, Tc2, NK-T (IL-4, IL-5, IL-9, IL-13, IL-31) EOS, B cells, Mast cells/BAS	Th17, ILC3, Tc17 (IL-17, IL-22, IL-23) NEU
ACD, acute phase of hypersensitivity pneumonitis, celiac disease, asthma, AR/ARC, CRS, AD, drug allergy (TEN, SJS, erythema multiforme)	Asthma, AR/CRS AD (T2 endotypes), EoE, food allergy, drug allergy (DRESS)	Neutrophilic asthma, AD, drug allergy (AGEP)



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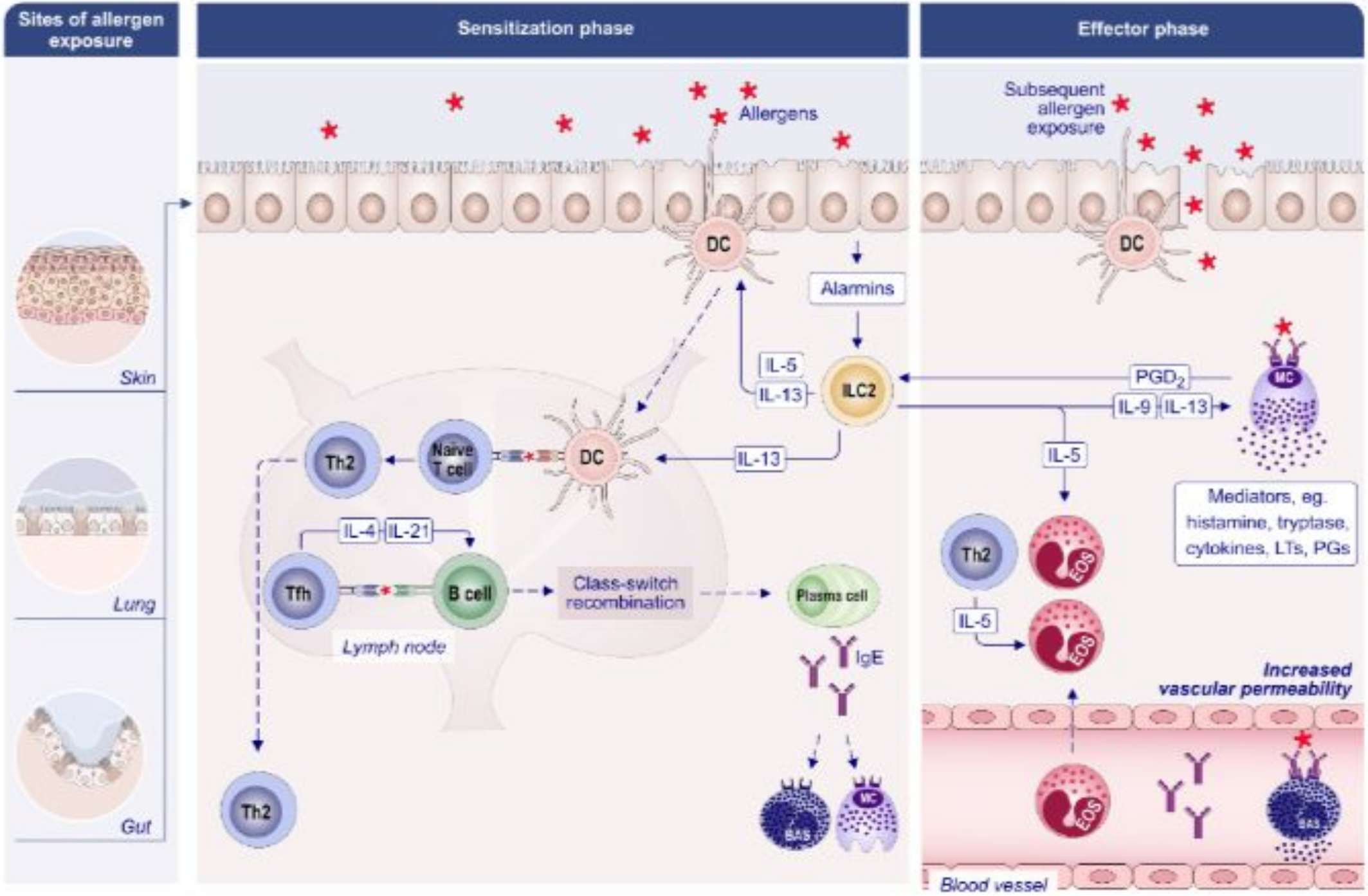

Sites of allergen exposure
Sensitization phase
Effector phase
Skin
Lung
Gut
Allergens
DC
Alarmins
IL-5
IL-13
ILC2
Th2
Naive T cell
DC
IL-13
IL-4
IL-21
Tfh
B cell
Class-switch recombination
Plasma cell
IgE
Lymph node
Th2
Subsequent allergen exposure
DC
PGD2
IL-9
IL-13
MC
IL-5
Mediators, eg. histamine, tryptase, cytokines, LTs, PGs
Th2
EOS
IL-5
EOS
Increased vascular permeability
EOS
BAS
Blood vessel

FIGURE 2 Mechanisms of type I hypersensitivity in AR, ARC, asthma, AD, acute urticaria/angioedema, food, venom and drug allergy. The allergen is deposited on the epithelial cells, in the respiratory tract, gut or skin. The sensitization phase occurs after the first contact with the allergen, APCs, for example, DCs, present the antigen to the naïve Th. ILC2 are activated by cytokines released by epithelial cells (called alarmins), such as IL-25, IL-33 and TSLP. Upon activation, they produce large amounts of type 2 cytokines, including IL-5, IL-9 and IL-13, further supporting the T2-cell response. Tfh help B cells to maturate and produce high-affinity sIgE. MC and BAS possess the high-affinity receptor for the Fc fragment of sIgE (FcεRI) and are coated with sIgE, thus concluding the sensitization phase. The effector phase occurs upon subsequent exposure to the same allergen. The allergen crosslinks sIgE bound to MC and BAS, triggering degranulation. MCs are located in various tissues throughout the body, while BAS circulate in the blood. Preformed mediators inside MC and BAS, like histamine, induce symptoms upon release into the microenvironment, like vasodilation, bronchial muscle contraction and increased mucus secretion. Eosinophils play a significant role in the delayed allergic response and the persistence of inflammation, engaging mechanisms related to type IVb hypersensitivity. Therefore, the mutual interaction between type I and IVb-related processes is vital to both the sensitization and the chronic phase. Asthma, AR, ARC and AD endotypes can show T2-type cytokine overexpression (IL-4, IL-5 and IL-13) and high serum sIgE levels. Food/venom/drug allergy can be induced directly by a trigger with a potentially life-threatening anaphylactic reaction. Acute urticaria/angioedema can be induced by allergens (e.g. foods, medications, insect bites or stings). B, B lymphocyte; BAS, basophil; DC, dendritic cell; EOS, eosinophil; IL, interleukin; ILC2, type 2 innate lymphoid cell; LT, leukotrienes; MC, mast cell; PG(D_2), prostaglandin (D_2); sIgE, allergen-specific immunoglobulin E; Tfh, T follicular helper cell; Th naïve/2, T helper lymphocyte naïve/type 2; TSLP, thymic stromal lymphopoietin.

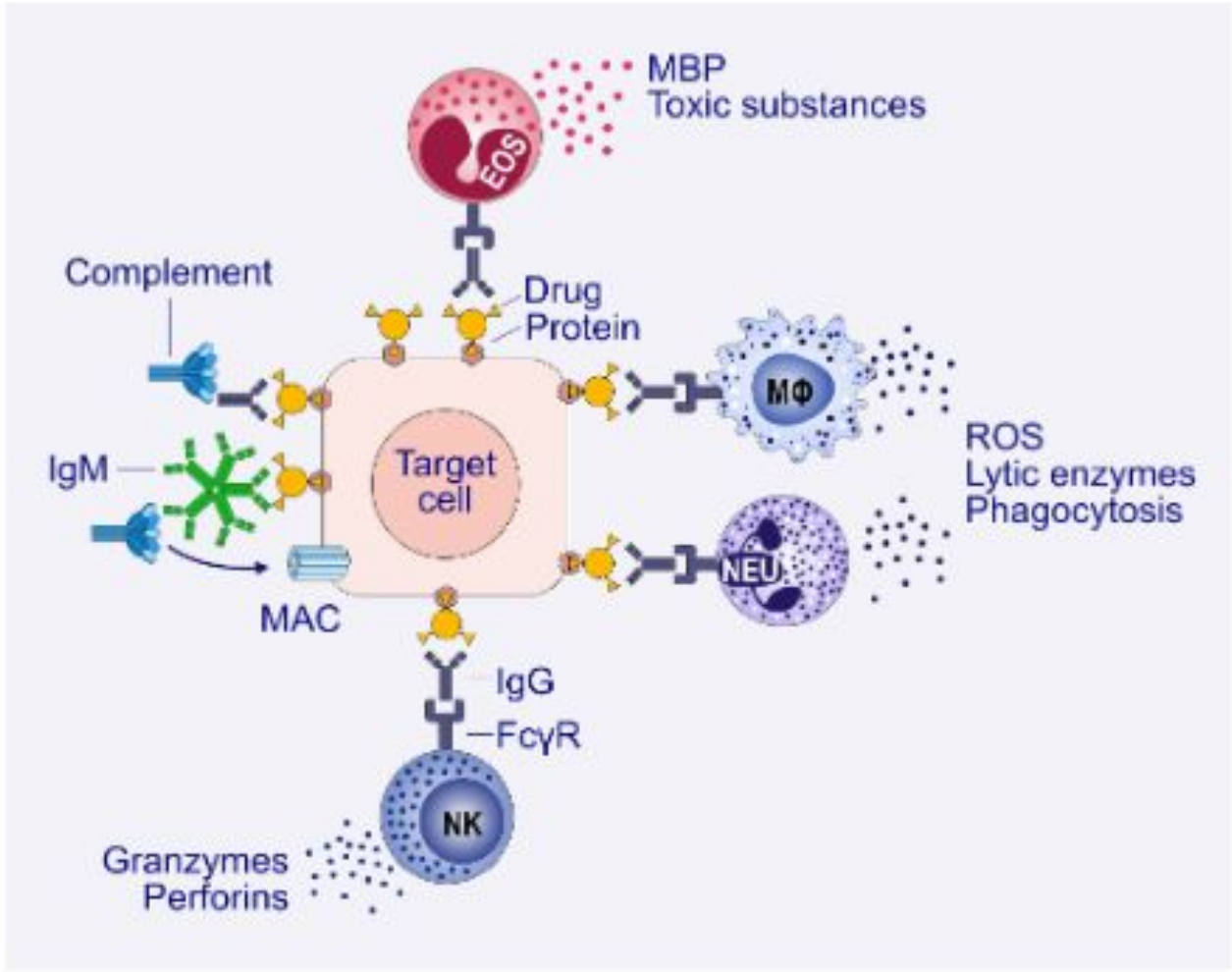


FIGURE 3 Mechanisms of type II hypersensitivity, that include allergic cytopenia. The drug binds to the cell membrane proteins, and subsequently, an anti-drug antibody (IgM or IgG), bind to the complex drug-cell membrane. This leads to complement activation and cell membrane lysis. IgG can be bound by FcγR on Mφ and NEU, which activates phagocytosis, ROS and enzymes production. IgG can be also bound by FcγR on EOS and cause the release of MBP or ROS. ADCC can be executed by NK or $CD8^+$ cells. The activation of complement and the recruitment of immune cells contribute to tissue damage. ADCC, Ab-dependent cellular cytotoxicity; EOS, eosinophil; FcγR, Fc fragment gamma receptor; IgG/M, immunoglobulin class G/M; MAC, membrane-attack complex; Mφ, macrophage; MBP, major basic protein; NEU, neutrophil; NK, natural killer cell; ROS, reactive oxygen species.

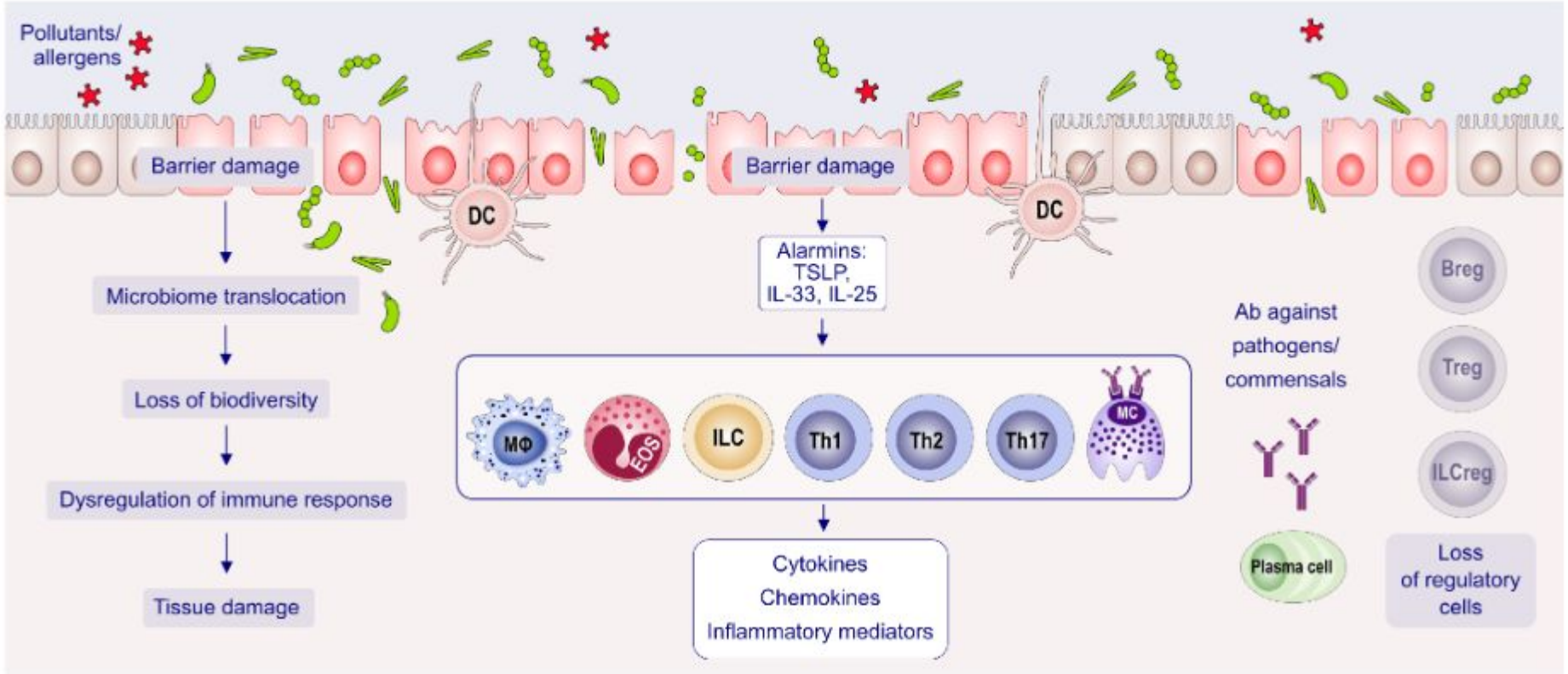


FIGURE 8 Mechanisms of type V hypersensitivity; include asthma, chronic AR/ARC, CRS, AD, FPIES, EoE and celiac disease. The epithelial barrier defect and microbial dysbiosis lead to dysregulation of the immune response, including extensive activation of T1, T2 and T17 responses combined with the loss of Treg, Bregs and ILCregs. Additionally, formation of sIgE to inhaled or ingested allergens, activation of Mφ, MC and BAS and release of proinflammatory cytokines, chemokines and inflammatory mediators (histamine, leukotrienes, ROS). The sequence of events eventually leads to tissue damage that can be seen in asthma, chronic AR/ARC, CRS, AD, FPIES, EoE and celiac disease. Immune response to opportunistic pathogens and commensals, for example, *Staphylococcus aureus* (microbiome translocation) leads to IgE antibody production against them. Ab, antibody; AD, atopic dermatitis; AR/ARC, allergic rhinitis/rhinoconjunctivitis; BAS, basophil; Breg, B regulatory cells; CRS, chronic rhinosinusitis; DC, dendritic cell; EOS, eosinophil; EoE, eosinophilic oesophagitis; IL, interleukin; ILC, innate lymphoid cell; ILCreg, ILC regulatory cells; MC, mast cell; Mφ, macrophage; FPIES, food protein-induced enterocolitis syndrome; ROS, reactive oxygen species; sIgE, allergen-specific immunoglobulins class E; Th1/2/17, T helper lymphocyte type 1/2/17; Treg, T regulatory cells; TSLP, thymic stromal lymphopoietin.

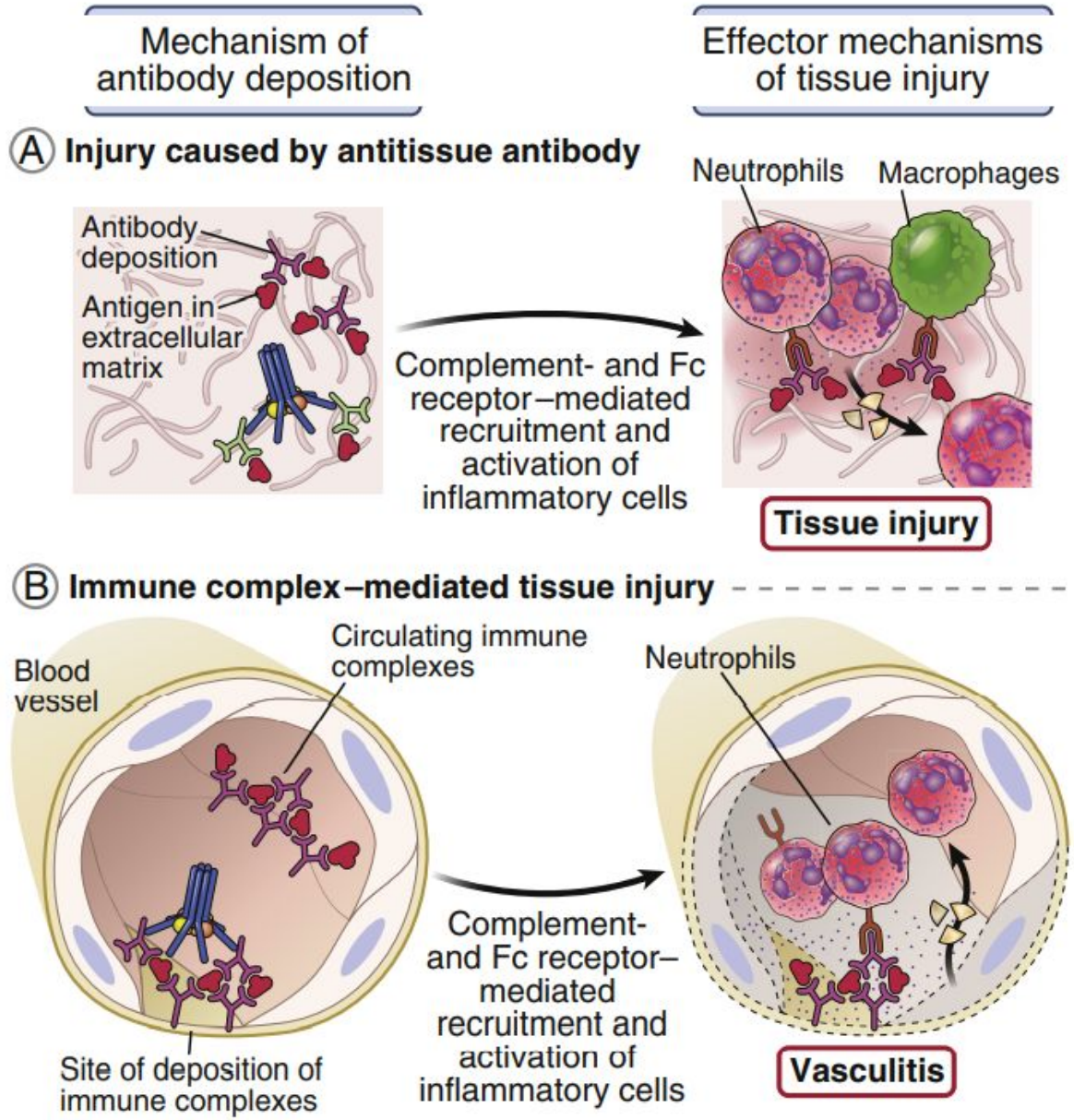


FIGURE 11-7 Types of antibody-mediated diseases. Antibodies (other than IgE) may cause tissue injury and disease by: **A,** binding directly to their target antigens on the surface of cells and in the extracellular matrix (type II hypersensitivity) or **B,** by forming immune complexes that deposit mainly in blood vessels (type III hypersensitivity).

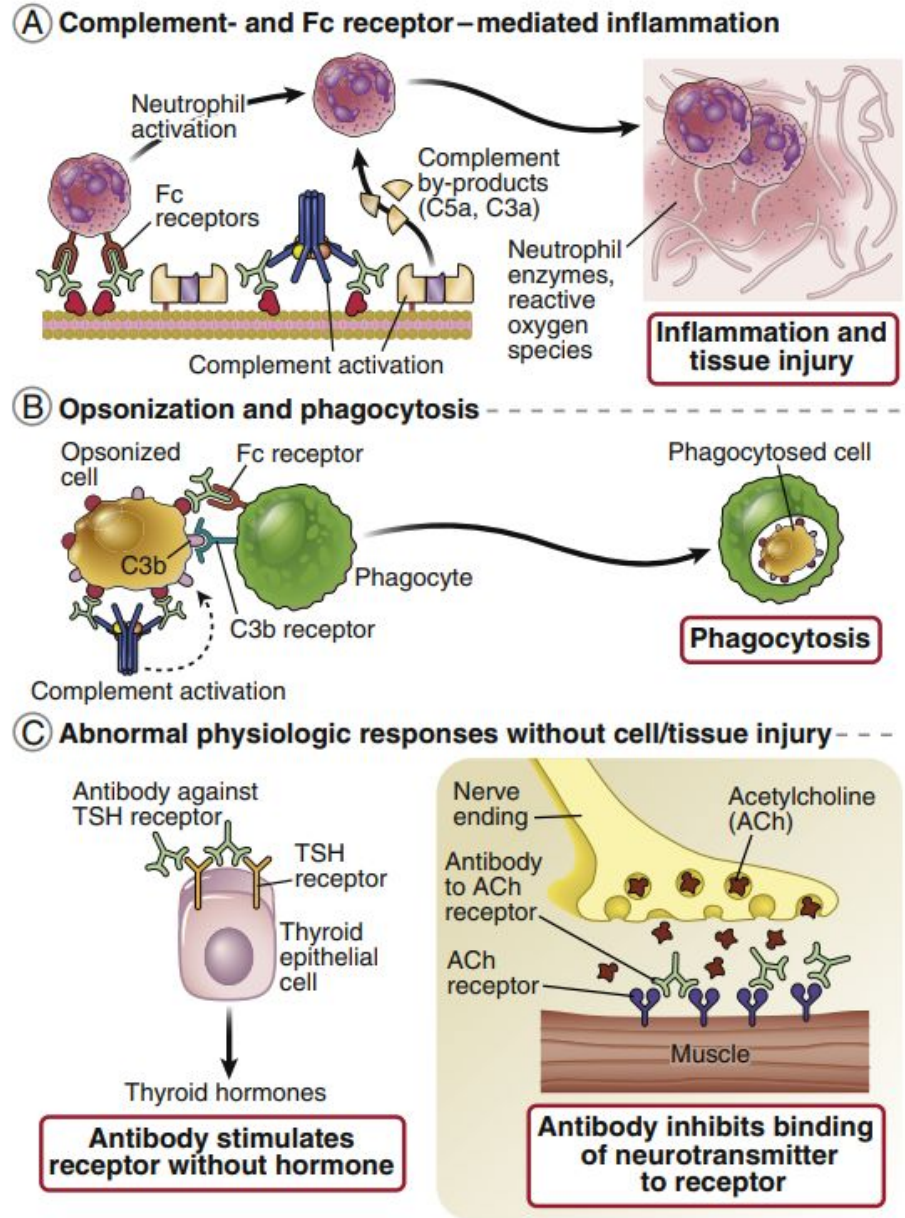


FIGURE 11-8 **Effector mechanisms of antibody-mediated diseases.** Antibodies cause disease by **A,** inducing inflammation at the site of deposition; **B,** opsonizing cells for phagocytosis; and **C,** interfering with normal cellular functions, such as hormone receptor signaling. All three mechanisms are seen with antibodies that bind directly to their target antigens, but immune complexes cause disease mainly by inducing inflammation (**A**). *TSH*, Thyroid-stimulating hormone.

Antibody-mediated disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune (idiopathic) thrombocytopenic purpura	Platelet membrane proteins (gpIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Goodpasture syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Graves disease (hyperthyroidism)	Thyroid stimulating hormone (TSH) receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetycholine binding, down-modulates receptors	Muscle weakness, paralysis
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (desmoglein)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia
Rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis

FIGURE 11-9 Human antibody-mediated diseases (type II hypersensitivity). The figure lists examples of human diseases caused by antibodies. In most of these diseases, the role of antibodies is inferred from the detection of antibodies in the blood or the lesions, and in some cases by similarities with experimental models in which the involvement of antibodies can be formally established by transfer studies.

Immune complex disease	Antibody specificity	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	In some cases, microbial antigens (e.g., hepatitis B virus surface antigen); most cases unknown	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s)	Nephritis
Serum sickness (clinical and experimental)	Various protein antigens	Systemic vasculitis, nephritis, arthritis
Arthus reaction (experimental)	Various protein antigens	Cutaneous vasculitis

FIGURE 11-10 Immune complex diseases (type III hypersensitivity). Examples of human diseases caused by the deposition of immune complexes, as well as two experimental models. In the diseases, immune complexes are detected in the blood or in the tissues that are the sites of injury. In all the disorders, injury is caused by complement-mediated and Fc receptor–mediated inflammation.

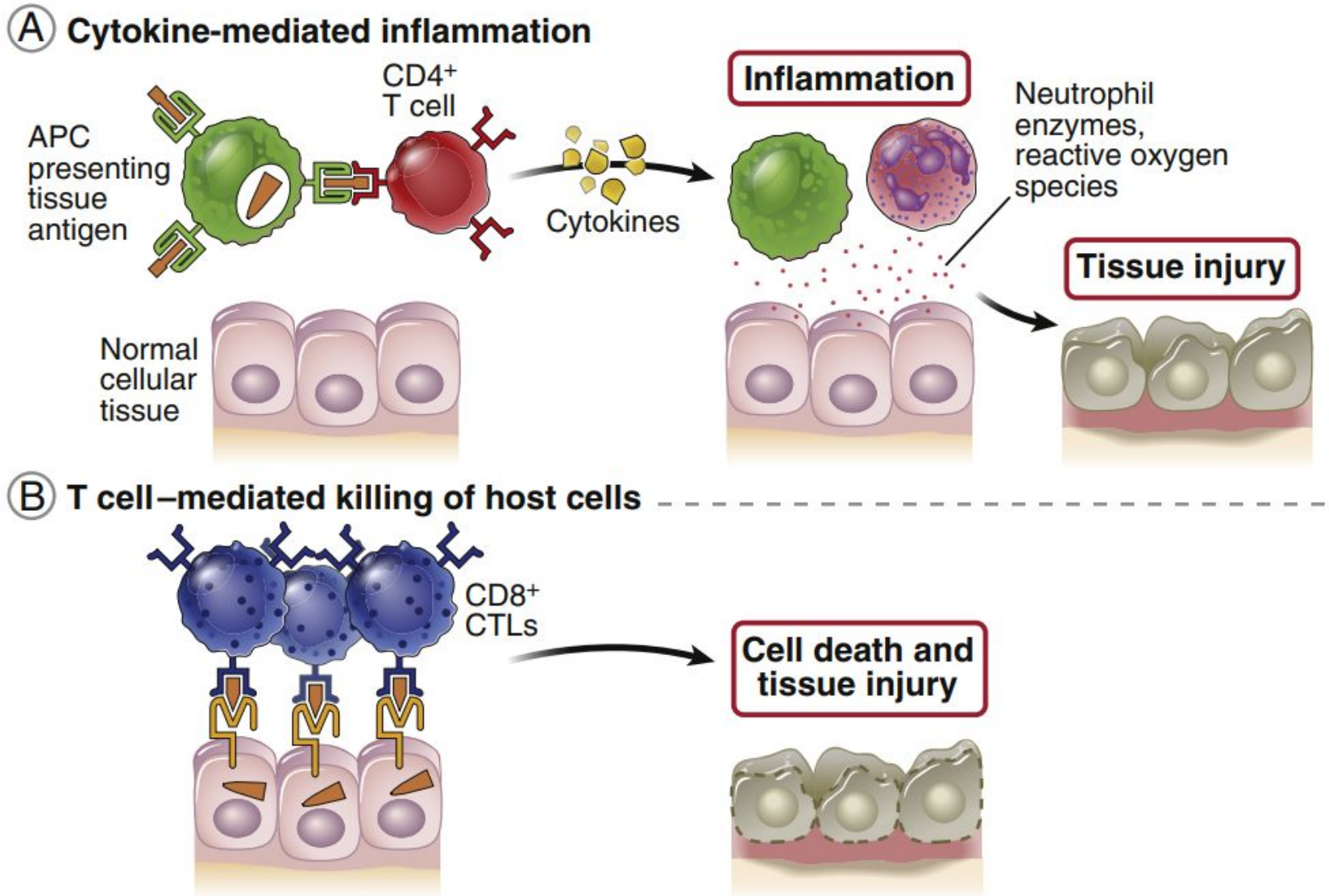


FIGURE 11-11 Mechanisms of T cell–mediated tissue injury (type IV hypersensitivity). T cells may cause tissue injury and disease by two mechanisms. **A,** Inflammation may be triggered by cytokines produced mainly by CD4+ T cells in which tissue injury is caused by activated macrophages and inflammatory cells; *APC*, Antigen-presenting cell. **B,** Direct killing of target cells is mediated by CD8+ cytotoxic T lymphocytes (CTLs).

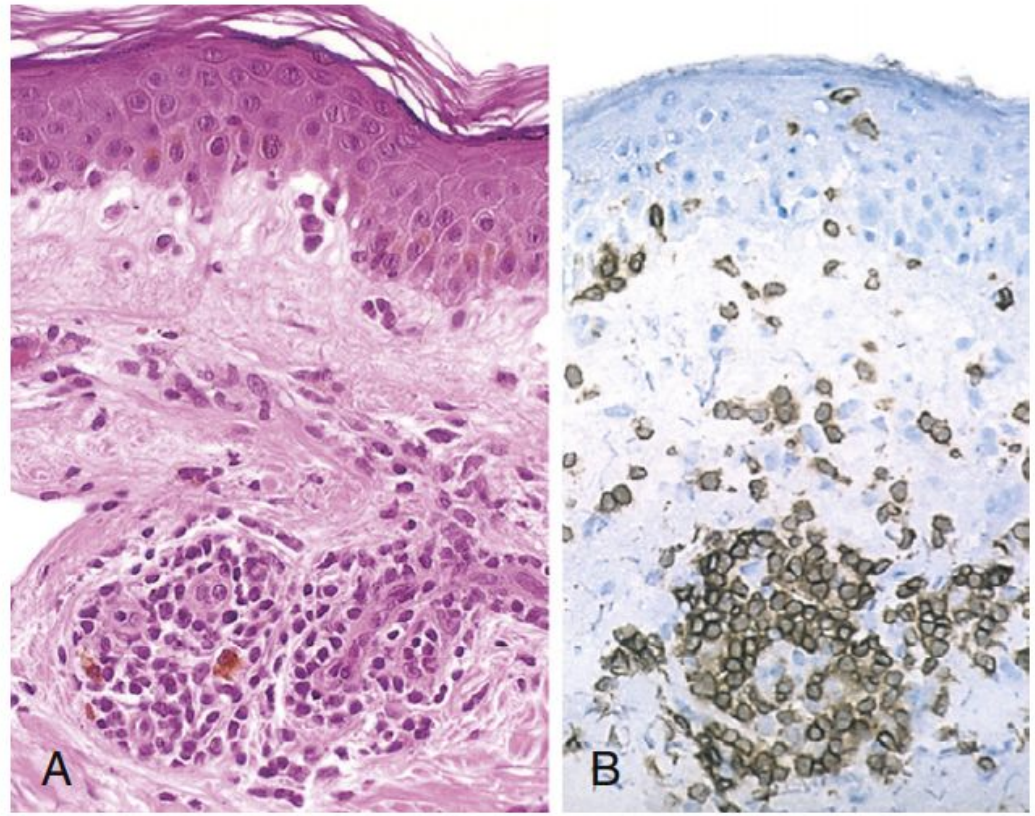


FIGURE 11-12 **Delayed-type hypersensitivity reaction in the skin. A,** Perivascular accumulation (cuffing) of mononuclear inflammatory cells (lymphocytes and macrophages), with associated dermal edema and fibrin deposition. **B,** Immunoperoxidase staining reveals a predominantly perivascular cellular infiltrate that marks positively with anti-CD4 antibodies. (**B,** Courtesy Dr. Louis Picker, Department of Pathology, Oregon Health Sciences University, Portland.)

Disease	Specificity of pathogenic T cells	Clinicopathologic manifestations
Multiple sclerosis	Myelin proteins	Demyelination in the central nervous system, sensory and motor dysfunction
Rheumatoid arthritis	Unknown antigens in joint	Inflammation of synovium and erosion of cartilage and bone in joints
Type 1 (insulin-dependent) diabetes mellitus	Pancreatic islet antigens	Impaired glucose metabolism, vascular disease
Crohn's disease	Unknown, ? role of intestinal microbes	Inflammation of the bowel wall; abdominal pain, diarrhea, hemorrhage
Contact sensitivity (e.g., poison ivy reaction)	Modified skin proteins	DTH reaction in skin, rash
Chronic infections (e.g., tuberculosis)	Microbial proteins	Chronic (e.g., granulomatous) inflammation
Viral hepatitis (HBV, HCV)	Virally encoded proteins	CTL-mediated hepatocyte death, liver dysfunction; fibrosis
Superantigen-mediated diseases (toxic shock syndrome)	Polyclonal (microbial superantigens activate many T cells of different specificities)	Fever, shock related to systemic inflammatory cytokine release

FIGURE 11-13 T cell–mediated diseases. Diseases in which T cells play a dominant role in causing tissue injury; antibodies and immune complexes may also contribute. Note that multiple sclerosis, rheumatoid arthritis, and type 1 diabetes are autoimmune disorders. Crohn's disease, an inflammatory bowel disease, is likely caused by reactions against microbes in the intestine and may have a component of autoimmunity. The other diseases are caused by reactions against foreign (microbial or environmental) antigens. In most of these diseases, the role of T cells is inferred from the detection and isolation of T cells reactive with various antigens from the blood or lesions, and from the similarity with experimental models in which the involvement of T cells has been established by a variety of approache diseases. The specificity of pathogenic T cells has been defined in animal models and in some of the human diseases. Viral hepatitis and toxic shock syndrome are disorders in which T cells play an important pathogenic role, but these are not considered examples of hypersensitivity. *CTL*, Cytotoxic T lymphocyte; *DTH*, delayed-type hypersensitivity; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus.

Fixed drug eruption

What is fixed drug eruption?

Fixed drug eruption is a distinctive cutaneous allergic reaction that characteristically recurs at the same site(s) on re-exposure to the medication or other chemical agent.

Who gets fixed drug eruption?

Fixed drug eruption affects both sexes, and affects adults more commonly than children. There are some examples of HLA-associations with fixed drug eruptions due to specific drugs eg, HLA-A30 with cotrimoxazole-induced fixed drug eruption.

What causes fixed drug eruption?

Fixed drug eruption is a delayed type IV hypersensitivity reaction. In the initial phase memory CD8+ T-cells at the dermo-epidermal junction release interferon-gamma when activated by the medication antigen causing epidermal basal layer damage. Recruited T-cells and neutrophils damage melanocytes and keratinocytes. During the resolution phase, dermal macrophages collect the melanin resulting in the typical post-inflammatory hyperpigmentation. Regenerating basal keratinocytes release interleukin-15 leading to the formation of resident memory CD8+ T-cells which remain quiescent but in a primed state ready to respond to the chemical antigen again.

Fixed drug eruption is usually due to oral medications, with antimicrobials and non-steroidal anti-inflammatory drugs (NSAID) being the most common culprits. Less common drug exposures may be topical or intravaginal. Fixed food eruptions may be due to antibiotics, flavouring or colouring agents, or preservatives in the food. Herbal supplements have also been implicated

What are the clinical features of fixed drug eruption?

Fixed drug eruption can be categorised by clinical morphology. The most common form is the localised pigmenting type; other presentations include bullous (localised or generalised), mucosal, non-pigmenting, or generalised.

Fixed drug eruption typically presents as a single (or small number of) well-defined, round or oval red or violaceous patch or plaque which may blister or ulcerate. It is usually asymptomatic but can be itchy or painful. Over the next few days and weeks, the surface may become scaly or crusted before peeling, and the colour fades to leave brown post-inflammatory hyperpigmentation. Post-inflammatory hyperpigmentation tends to be more prominent in skin of colour.

In contrast to many other drug eruptions, the patient remains systemically well.

The hands and feet, eyelids, and anogenital areas are common sites. Lesions in the oral mucosa are usually found on the lips, tongue and hard palate. A fixed drug eruption may occur at the same location as previous skin trauma such as a burn, insect bite, or venepuncture.

On the first occasion, the eruption may develop after weeks to years of regular ingestion of the drug, but subsequent episodes develop within minutes to hours of recommencing the implicated drug. A patch of fixed drug eruption shows a refractory period during which it will not flare even with re-exposure. With subsequent episodes, the original patch may enlarge and more patches may appear. The post-inflammatory hyperpigmentation darkens with each recurrence.

Clinical variants of fixed drug eruption

Mucosal fixed drug eruption

- Involves lips, tongue, hard palate, genital mucosa
- Blisters and erosions are common
- Can be isolated/localised or may occur with cutaneous lesions
- Oral mucosal lesions commonly due to cotrimoxazole and naproxen
- Genital mucosal lesions: glans penis – cotrimoxazole; vulva – NSAIDs.

Non-pigmenting fixed drug eruption

- Often symmetrical lesions
- Resolves without post-inflammatory hyperpigmentation
- Associated with piroxicam and pseudoephedrine.

Generalised fixed drug eruption

- Presents with numerous lesions
- Lesions may be targetoid resembling erythema multiforme.

Generalised bullous fixed drug eruption

- Rare variant
- Recurrent episodes with onset within 24 hours of drug exposure
- Numerous large blisters and erosions with normal skin between typically affecting <10% of the skin surface
- Relative sparing of mucosal surfaces
- Lesions are not targetoid
- Fever, malaise and arthralgia may be associated
- Resolves with post-inflammatory hyperpigmentation.

What are the complications of fixed drug eruption?

- Blisters and erosions
- Post-inflammatory hyperpigmentation
- Recurrence
- Cross-reaction with other medications
- Generalised bullous fixed drug eruption can be complicated by fluid loss, electrolyte imbalance, and secondary infection.

How is fixed drug eruption diagnosed?

Fixed drug eruption should be considered on history and examination but may be difficult on the first occasion. On subsequent episodes, a detailed history of oral intake in the preceding 24 hours may identify the culprit.

Investigations may include:

Skin biopsy — shows an interface dermatitis in an early lesion with scattered apoptotic keratinocytes, vacuolar degeneration, dermal oedema, and a superficial perivascular lympho-eosinophilic infiltrate. Blisters are subepidermal if present. A late lesion shows upper dermal melanophages.

Oral challenge test — with a low dose of the suspected drug although there is typically a refractory period during which time the patch will not flare. This is contraindicated in patients with generalised bullous fixed drug eruption.

Patch test — using the suspected drug in soft paraffin applied to the lesion site is positive in 50% of cases. Prick testing and patch testing on normal skin is usually negative.

What is the differential diagnosis for fixed drug eruption?

- First episode of single or few lesions — bullous insect bite reaction, bullous pemphigoid and other autoimmune bullous disorders
- Targetoid lesions — erythema multiforme
- Multiple bullous lesions — Stevens-Johnson syndrome/toxic epidermal necrolysis
- Oral lesions — herpes simplex, aphthous ulcer, oral autoimmune blistering diseases

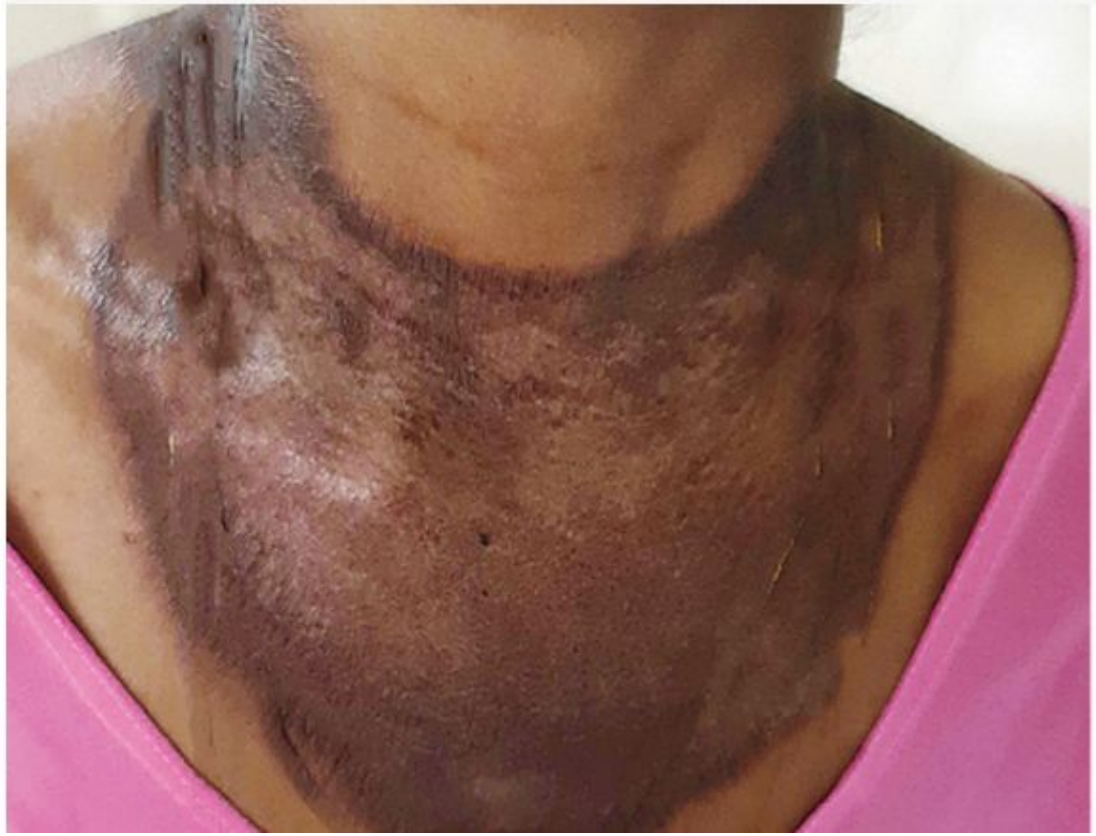
What is the treatment for fixed drug eruption?

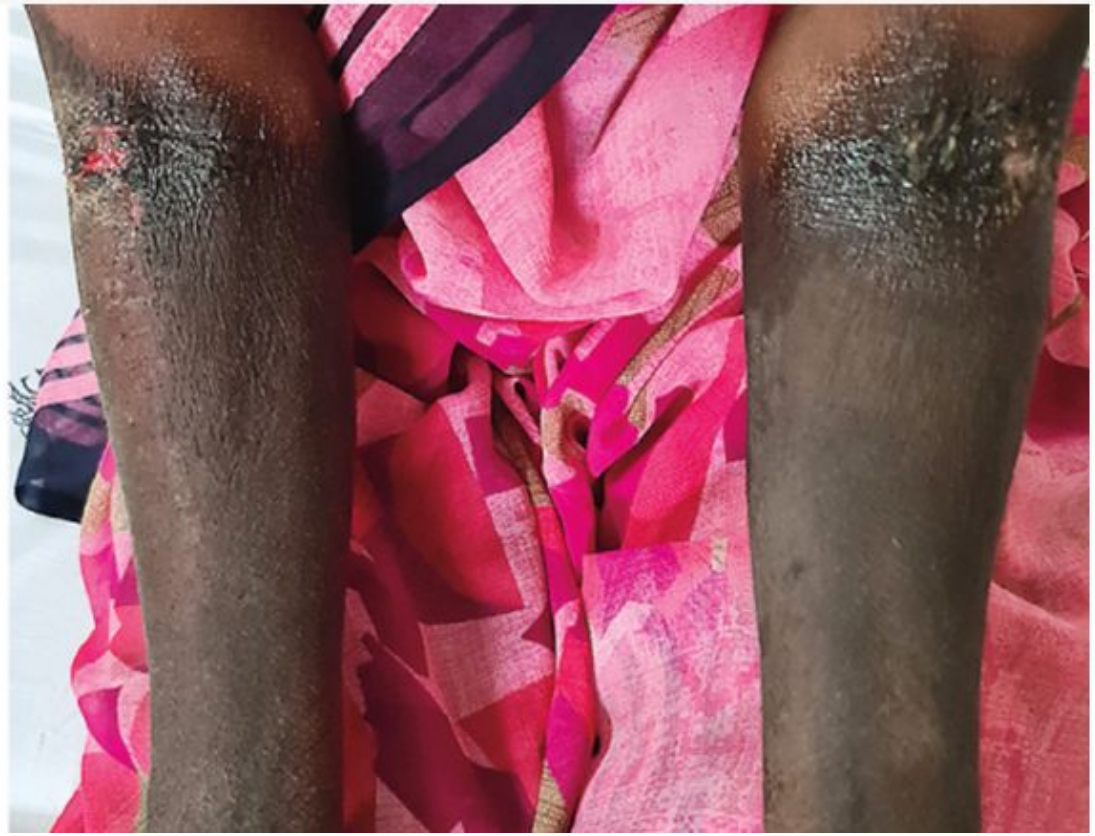
- Discontinuation of suspected medication
- Avoiding implicated medication indefinitely
- Topical steroids/systemic corticosteroids
- Generalised bullous fixed drug eruption requires intensive care or burns unit

What is the outcome for fixed drug eruption?

Fixed drug eruption is generally a benign self-resolving eruption that recurs on re-exposure, leaving post-inflammatory hyperpigmentation. Subsequent flares can be more severe.

Generalised bullous fixed drug eruption can be life-threatening, and has been reported to have a 20% mortality rate.





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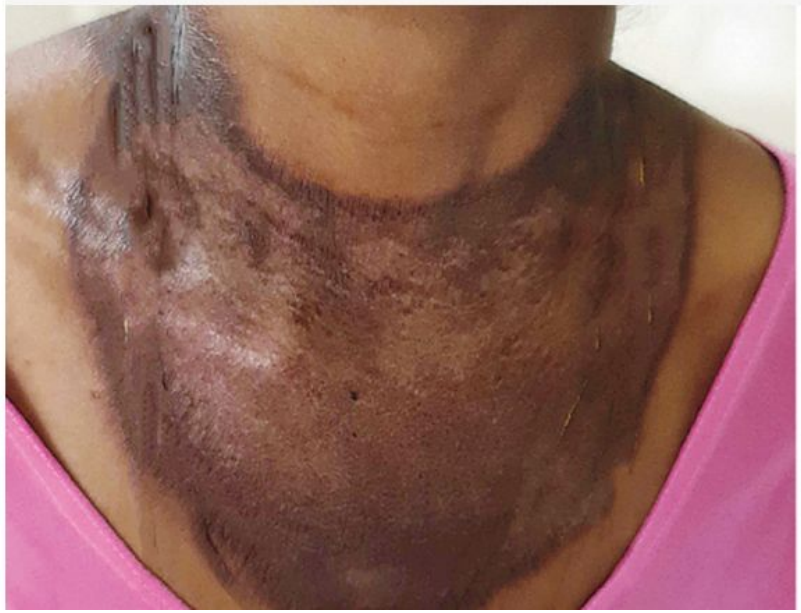

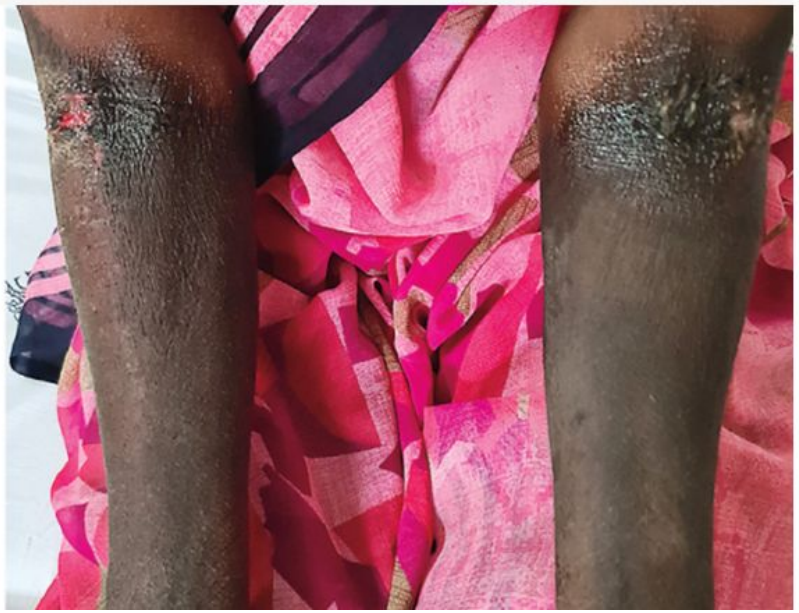

Correct!

A diagnosis of pellagra, or niacin deficiency, was made on the basis of the patient's diarrhea and symmetric, photosensitive dermatitis, including a typical Casal's necklace rash. After the patient was treated with vitamin B complex supplementation, the diarrhea resolved and the skin hyperpigmentation was reduced.

- Cobalamin (vitamin B12) deficiency
- **Pellagra** ✓
- Phytophotodermatitis
- Porphyria cutanea tarda
- Zinc deficiency

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SUMMARY

- Immune responses that cause tissue injury are called hypersensitivity reactions, and the diseases caused by these reactions are called hypersensitivity diseases or immune-mediated inflammatory diseases.
- Hypersensitivity reactions may arise from uncontrolled or abnormal responses to foreign antigens or autoimmune responses against self antigens.
- Hypersensitivity reactions are classified according to the mechanism of tissue injury.
- Immediate hypersensitivity (type I, commonly called allergy) is caused by the activation of Th2 cells and IL-4-producing Tfh cells and production of IgE antibody against environmental antigens or drugs (allergens), sensitization of mast cells by the IgE, and degranulation of these mast cells on subsequent encounter with the allergen.

- Clinico-pathologic manifestations of immediate hypersensitivity result from the actions of mediators secreted by the mast cells: amines dilate vessels and contract smooth muscles, arachidonic acid metabolites also contract muscles, and cytokines induce inflammation, the hallmark of the late-phase reaction. Treatment of allergies is designed to inhibit the production of mediators, antagonize their actions, and counteract their effects on end organs.
- Antibodies against cell and tissue antigens may cause tissue injury and disease (type II hypersensitivity). IgM and IgG antibodies promote the phagocytosis of cells to which they bind, induce inflammation by complement-mediated and Fc receptor–mediated leukocyte recruitment, and may interfere with the functions of cells by binding to essential molecules and receptors.
- In immune complex diseases (type III hypersensitivity), antibodies may bind to circulating antigens to form immune complexes, which deposit in vessels, leading to inflammation in the vessel wall (vasculitis), which secondarily causes tissue injury due to impaired blood flow.
- T cell–mediated diseases (type IV hypersensitivity) result from inflammation caused by cytokines produced by CD4+ Th1 and Th17 cells, or killing of host cells by CD8+ CTLs.

REVIEW QUESTIONS

1. What are the major types of hypersensitivity reactions?

2. What types of antigens may induce immune responses that cause hypersensitivity reactions?

3. What is the sequence of events in a typical immediate hypersensitivity reaction? What is the late-phase reaction, and how is it caused?

4. What are some examples of immediate hypersensitivity disorders, what is their pathogenesis, and how are they treated?

5. How do antibodies cause tissue injury and disease?

6. What are some examples of diseases caused by antibodies specific for cell surface or tissue matrix antigens?

7. How do immune complexes cause disease, and how are the clinical manifestations different from most diseases caused by antibodies specific for cell surface or tissue matrix proteins?

8. What are some examples of diseases caused by T cells, what is their pathogenesis, and what are their principal clinical and pathologic manifestations?