FARMAKOTERAPI OBAT pada SISTEM IMUN

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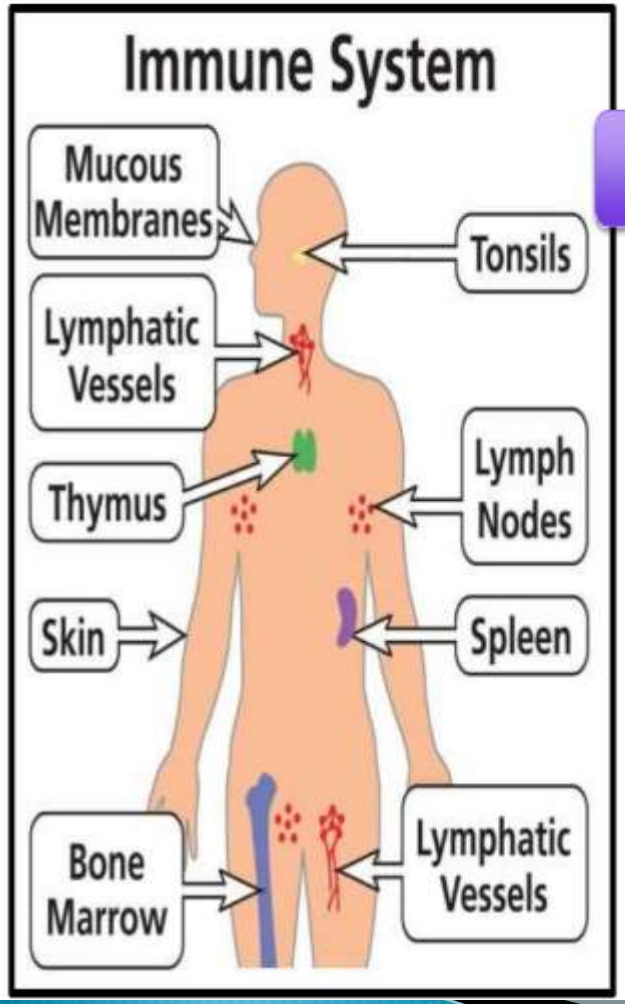
DEFINITION

Sistem imun melindungi individu dari patogen berupa virus, mikroorganisme dan parasit. Besarnya respon imun tergantung kemapuan sistem untuk mengenali (**recognize) molekul asing** (antigens), dan kemudian memberikan reaksi yang sesuai untuk mengeliminasi sumber antigen.

SISTEM IMUN



1 → Tahap 1 Perlindungan Luar

2 → Tahap 2 Perlindungan system imun non spesifik

3 → Tahap 3 Perlindungan respon imun spesifik

Sistem Imun Manusia

Ciri-ciri	Pembatas luar	Imunitas Bawaan	Imunitas Adaptif (Didapat)
Tingkat pertahanan	Lini pertama pertahanan terhadap infeksi dan kerusakan jaringan	Lini kedua pertahanan sebagai respons terhadap kerusakan jaringan dan infeksi (respons inflamasi)	Lini ketiga pertahanan yang dimulai ketika sistem imunitas bawaan menyampaikan sinyal kepada sel-sel imunitas adaptif
Waktu respons	Konstan	Respons segera	Ada jeda waktu (tertunda) antara terjadinya paparan antigen primer (pertama kali) dengan respons maksimal; respons segera terjadi setelah paparan antigen sekunder (paparan kedua kali atau berikutnya)
Spesifisitas	Luas	Luas	Respons sangat spesifik terhadap "antigen"
Sel-sel	Sel-sel epietel Mikrobiom	Sel mast, granulosit (neutrofil, eosinofil, basofil), monosit/ makrofag, sel-sel *natural killer* (NK), trombosit, sel-sel endotel	LimfositT, limfositB, makrofag, sel-sel dendritik
Memori	Tidak melibatkan memori	Tidak melibatkan memori	Memori imunologis spesifik oleh limfosit T dan B
Molekul aktif	Defensin, katelisidin, kolektin, laktoferin, toksin bakteri	Komplemen, faktor pembekuan, kinin, sitokin	Antibodi, komplemen, sitokin
Proteksi	Perlindungan termasuk pembatas anatomis (yaitu kulit dan membran mukosa), sel-sel dan molekul sekresi (misalnya, lisozim, pH lambung yang asam dan urin), dan aktivitas *cilia*	Perlindungantermasukrespons vaskular, komponen selular (misalnya, sel-sel mast, neutrofil, makrofag), molekul- sekresi atau sitokin, dan aktivasi sistem protein plasma	Perlindungan termasuk limfosit T dan B yang teraktivasi, sitokin, dan antibodi

PERLINDUNGAN LUAR

1

Peran perlindungan luar
= Lapisan Permukaan

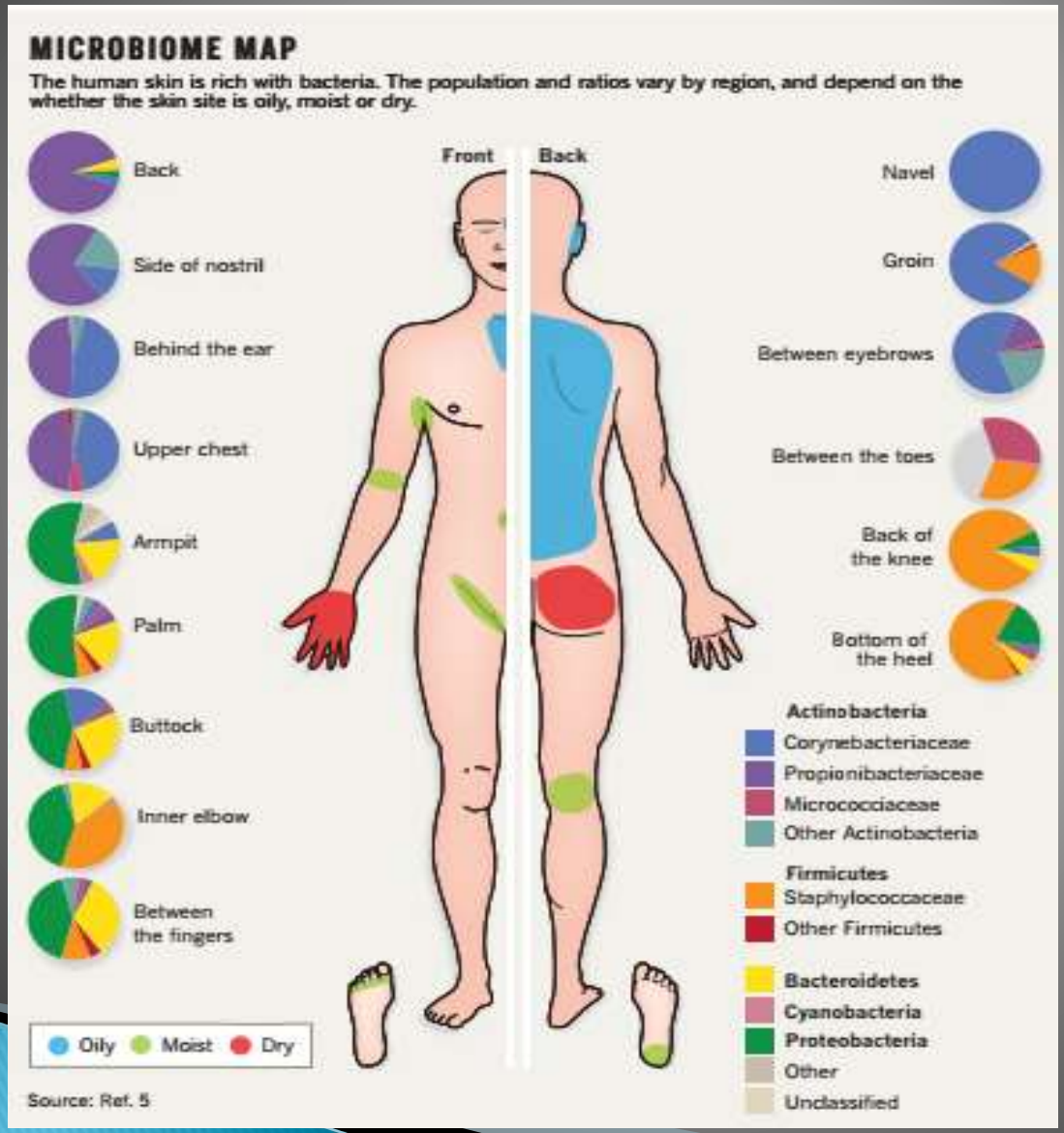
Kulit

Mukosa

Apakah yang ada di sana?

https://microbiologysociety.org/why-microbiology-matters/what-is-microbiology/microbes-and-the-human-body/immune-system.html

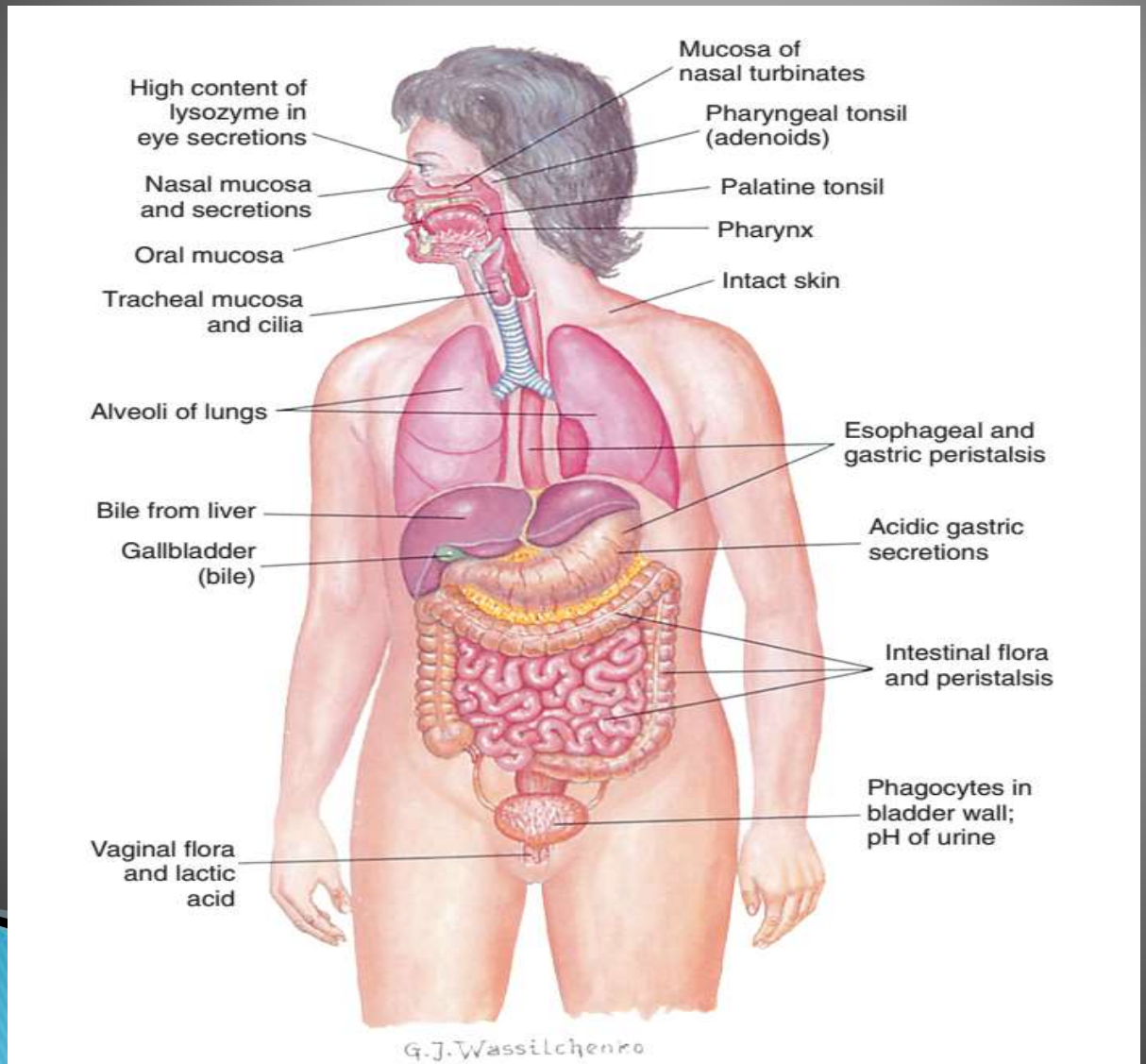
KULIT MENGANDUNG MIKROBA



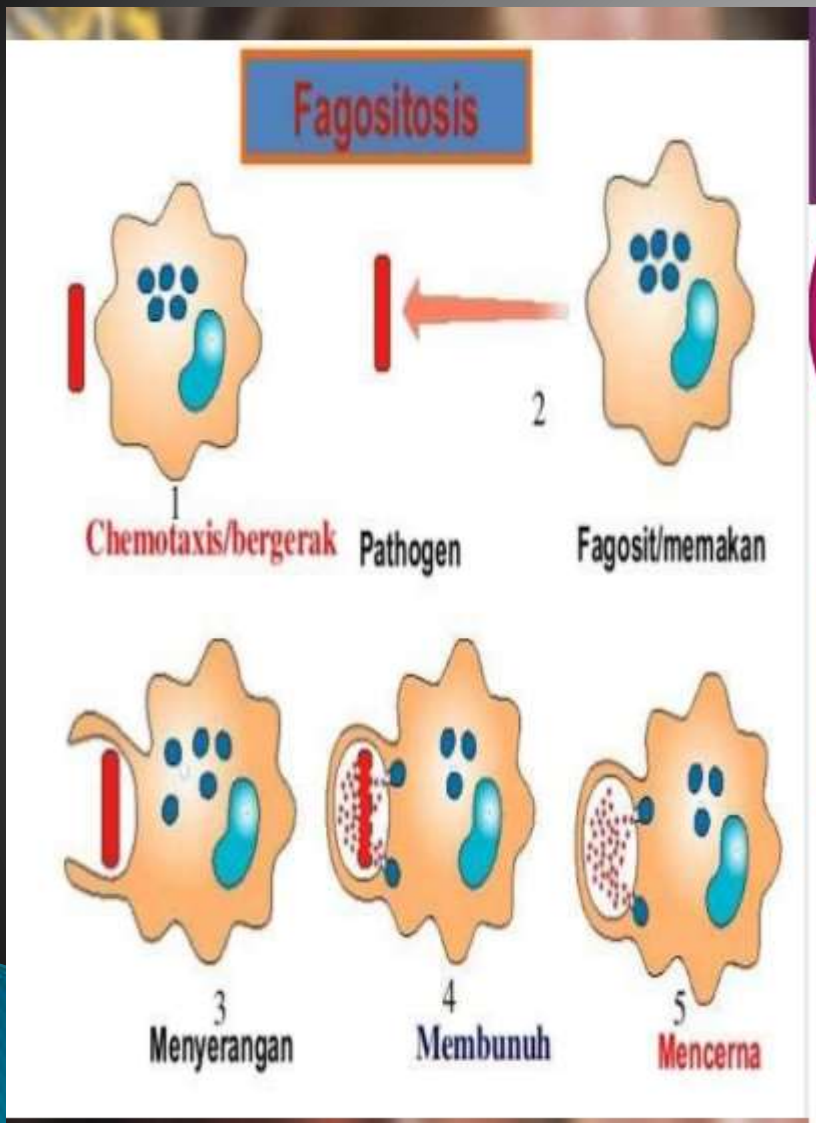
Lokasi	Mikroorganisme
Skin	Kebanyakan kokusdan batang gram-positif, *Staphylococcus epidermidis, corynebacteria, mycobacteria,* dan streptokokus merupakan jenis paling banyak; *Staphylococcus aureus* pada beberapa individu; juga ragi *(Candida, Pityrosporum)* pada beberapa daerah di kulit
	Beberapa mikroorganisme hidup dan tinggal di kulit untuk sementara
	Pada bagian kulit yang lembab, bakteri gram-negatif
	Di sekitar kelenjar sebaseus, *Propionibacterium* dan *Brevibacterium*
	Kutu *Demodex folliculorum* tinggal di folikel rambut dan kelenjar sebaseus di wajah
Hidung	Kebanyakan kokus dan batang gram-positif, khususnya *S. epidermidis*
	Beberapa individu pembawa bakteri patogen di hidung, termasuk *S. aureus,* streptokokus β-hemolitik, dan *Corynebacterium diphtheria*
Mulut	Kompeks bakteri yang meliputi beberapa spesies streptokokus, *Actinomyces,* lactobacilli, dan *Haemophilus*
	Bakteri anaerob dan spirochete mengkolonisasi celah gingiva
Faring	Seperti flora mulut ditambah staphylococci, *Neisseria,*dan diphtheroid
	Beberapa individu tanpa gejala membawa bakteri patogen: *pneumococcus, Haemophilus influenzae, Neisseria meningitidis,* dan *C. diphtheria*
Usus kecil distal	Enterobakteri, streptococci, lactobacilli, bakteri anaerob, dan *C. albicans*
Kolon	*Bacteroides, lactobacilli, clostridia, Salmonella, Shigella, Klebsiella, Proteus, Pseudomonas, enterococci,*dan streptokokus lainnya, *bacilli,* dan *Escherichia coli*
Uretra distal	Beberapa bakteri tertentu ditemukan pada kulit, khususnya *S. epidermidis* dan *diphtheroid*; juga *lactobacilli* dan streptokokus nonpatogen
Vagina	Sejak lahir hingga 1 bulan: seperti dewasa
	1 bulan hingga pubertas: *S. epidermidis, diphtheroid, E. coli,* dan streptokokus
	Pubertas sampai menopause: *Lactobacillus acidophilus,* diphtheroid, *staphylococci,* streptokokus, dan berbagai anaerob
	Pascamenopause: seperti pada prepubertas

Adaptasi dari Bennett JE et al, editor: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

Pertahanan Mukosa



SISTEM IMUN NON SPESIFIK



2

Peran perlindungan system imun non-spesifik (Fagostosis/sel imun memakan zat asing)

Sirkulasi darah

Sirkulasi limfatik

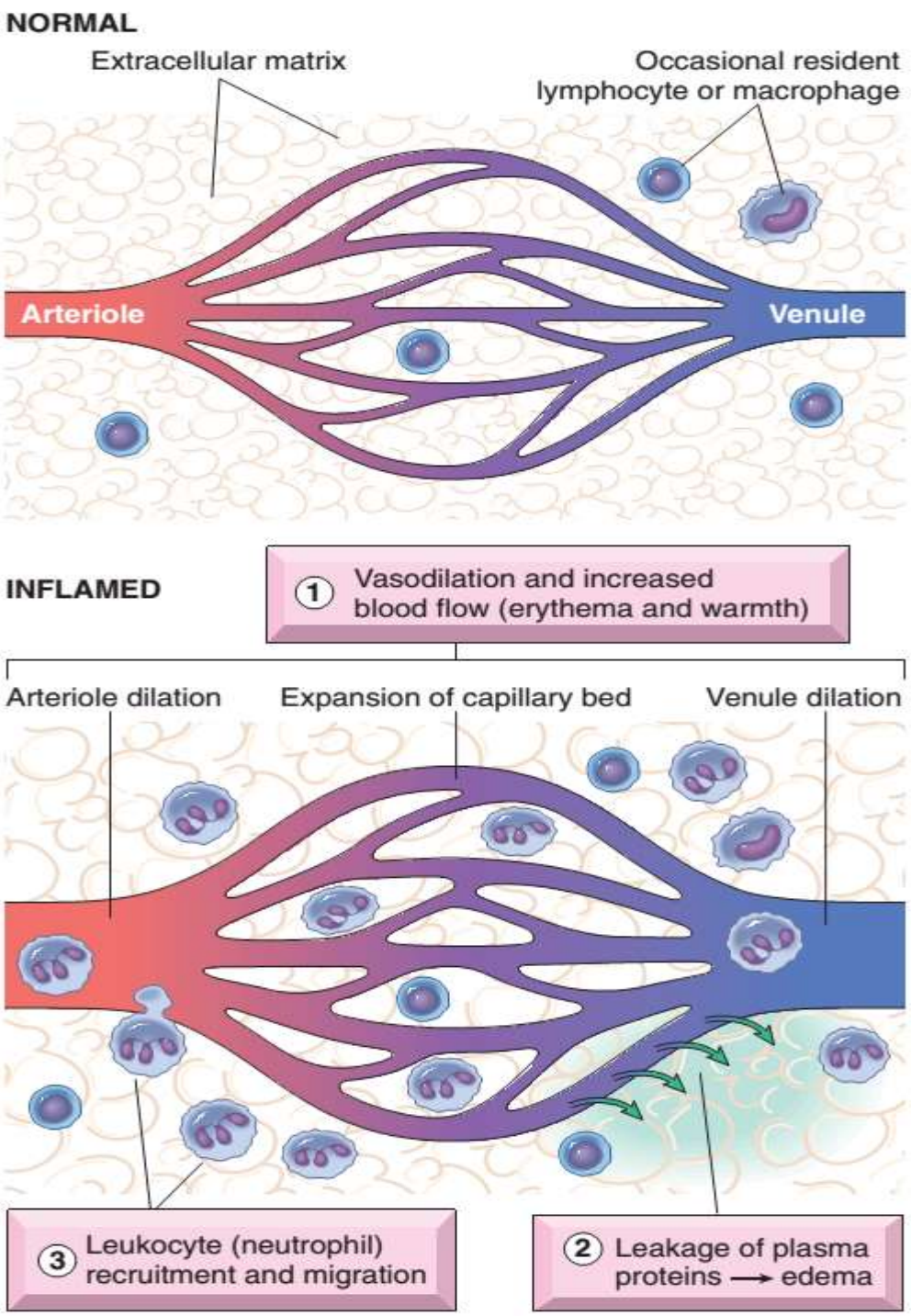
Dan di seluruh tubuh

https://microbiologysociety.org/why-microbiology-matters/what-is-microbiology/microbes-and-the-human-body/immune-system.html

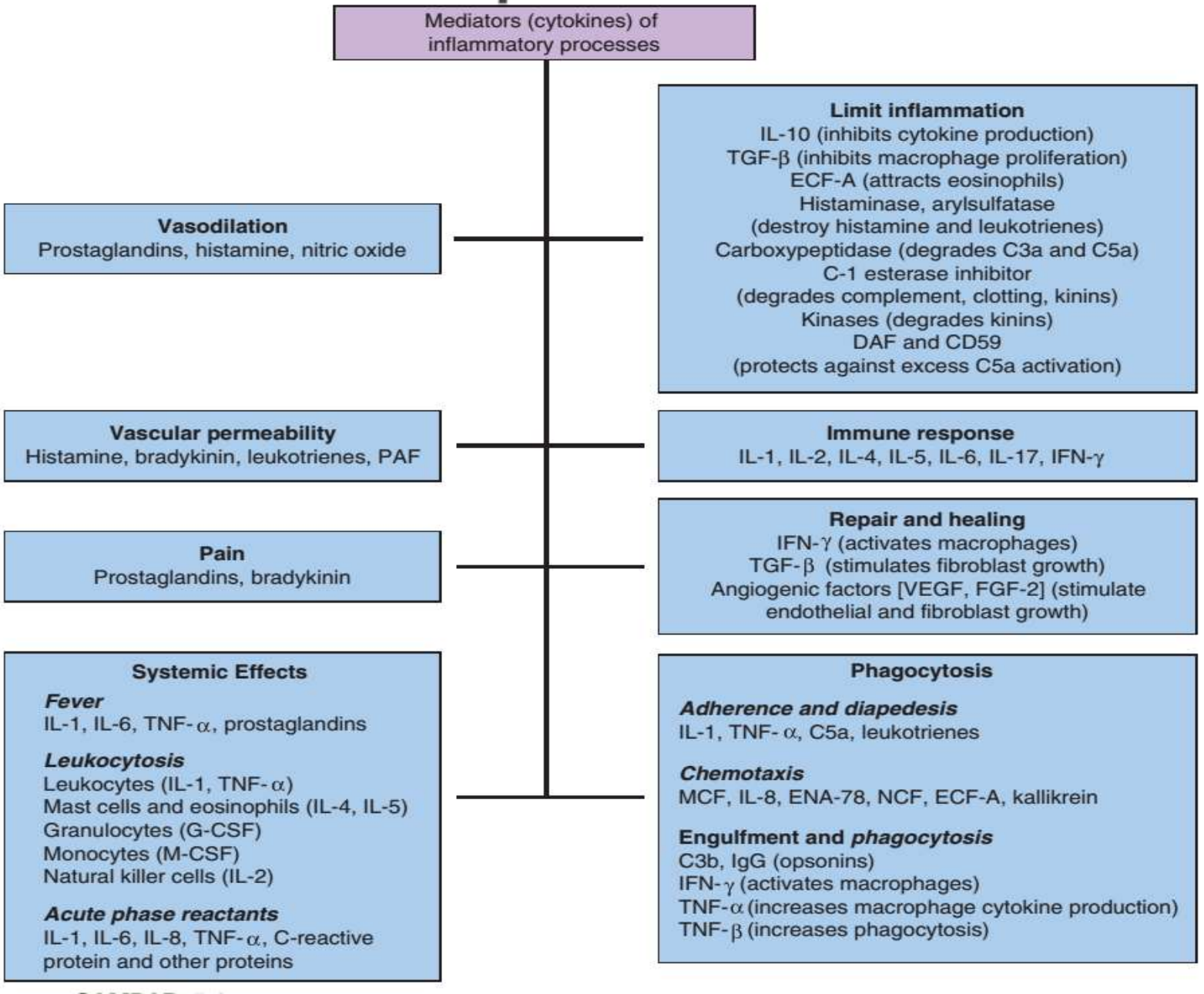
Inflamasi

- Manfaat :

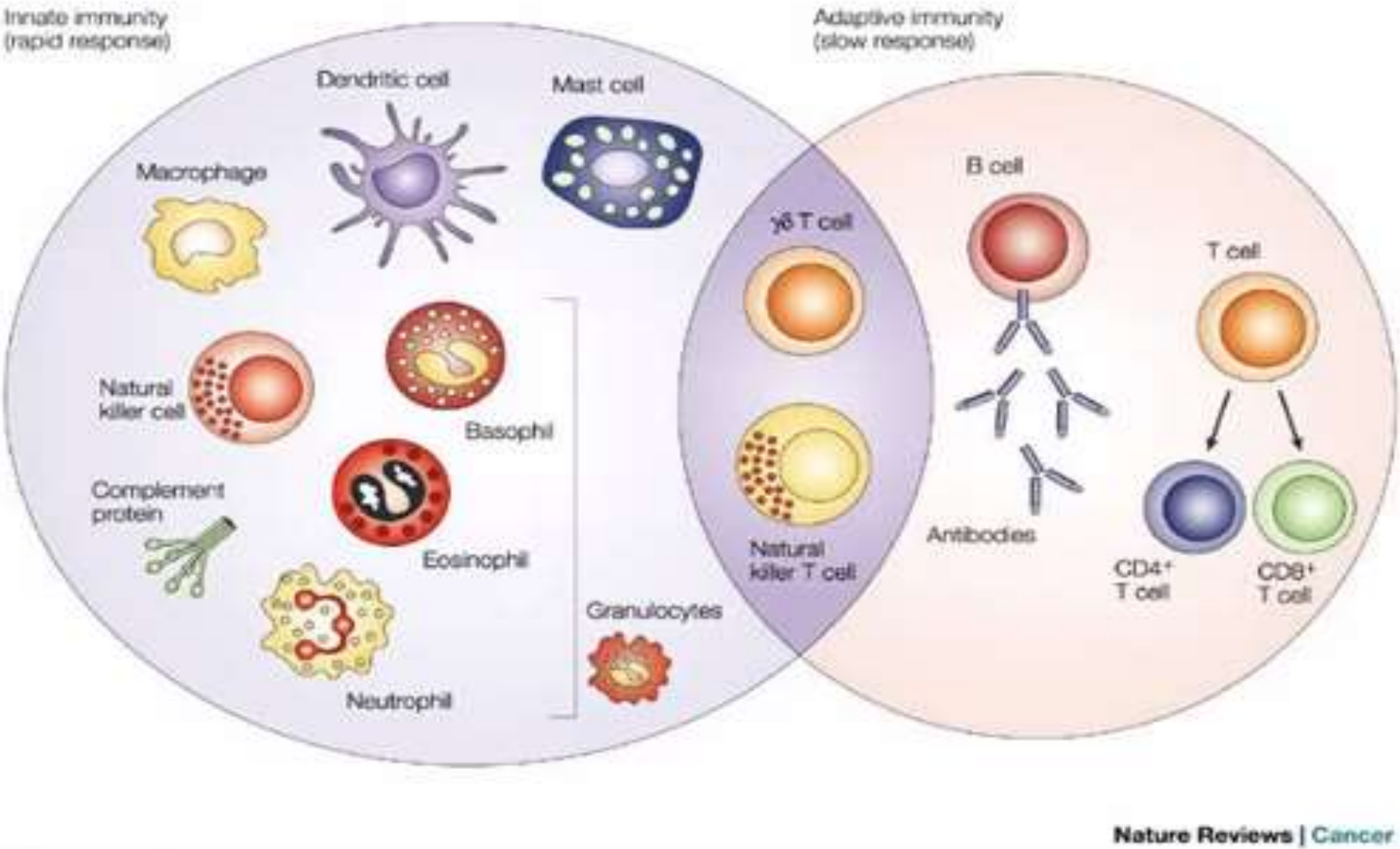
1. Mencegah infeksi dan kerusakan lbh lanjut
2. Membatasi & mengntrol proses inflamasi
3. Berinteraksi dg komp sist imun adaptif—respon lbh spesifik thd pathogen
4. Menyiapkan proses penyembuhandan perbaikan, serta menghilangkan debris akibat inflamasi



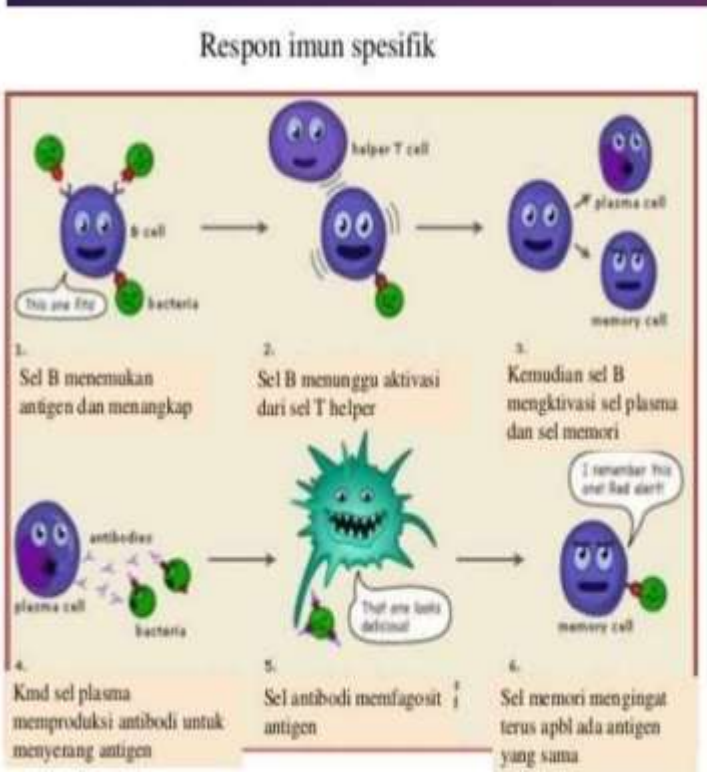
Mediator Utama pada Inflamasi



Human Immunity



SISTEM IMUN SPESIFIK



3

Peran perlindungan System Imun Spesifik (Pembentukan antibodi)

Sirkulasi darah

Sirkulasi limfatik

Dan di seluruh tubuh

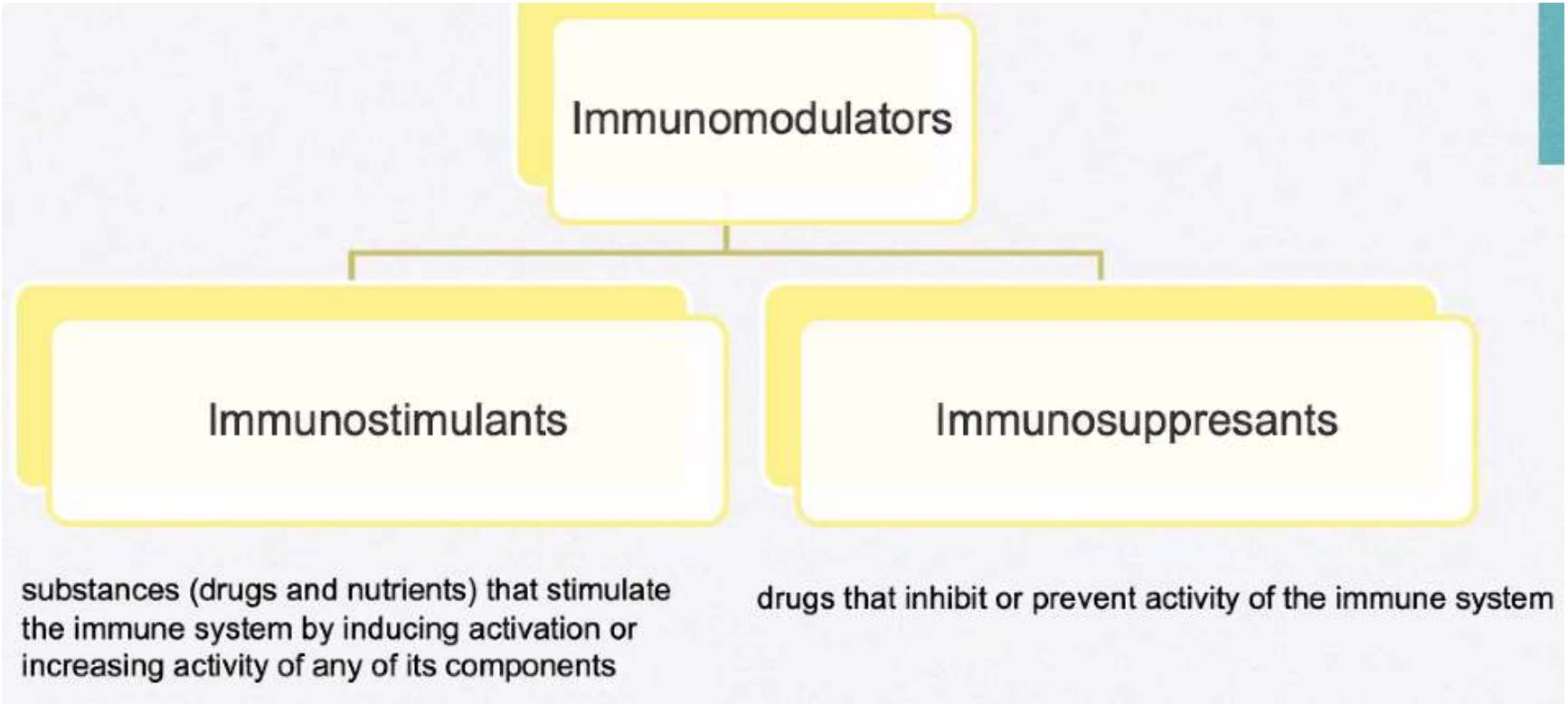
https://microbiologysociety.org/why-microbiology-matters/what-is-microbiology/microbes-and-the-human-body/immune-system.html

IMMUNOFARMAKOLOGI

- Immunofarmakologi : ilmu yang mempelajari tentang bagaimana mengontrol (menekan / meningkatkan) respon imun dengan mediator biologis ataupun khemis

- Immunomodulator : obat yang memodulasi sistem imun
  - Obat Immunosupressan : obat yg digunakan pd keadaan overaktivasi sistem imun (penyakit autoimun, post transplantasi)
  - Obat Immunostimulan : obat yang dapat meningkatkan status imun pada keadaan immunodefisiensi, HIV-AIDS, kanker
  - Obat Immunorestorasi : yang mengembalikan system imun yang terganggu dg memberikan bbrp komponen system imun spt Immune serum globulin (ISG), Hyperimmune Serum Globulin (HSG), plasmapharesis, leukophoresis, transplantasi sumsum tulang

IMMUNOMODULATOR



Non-Spesific Immunomodulators

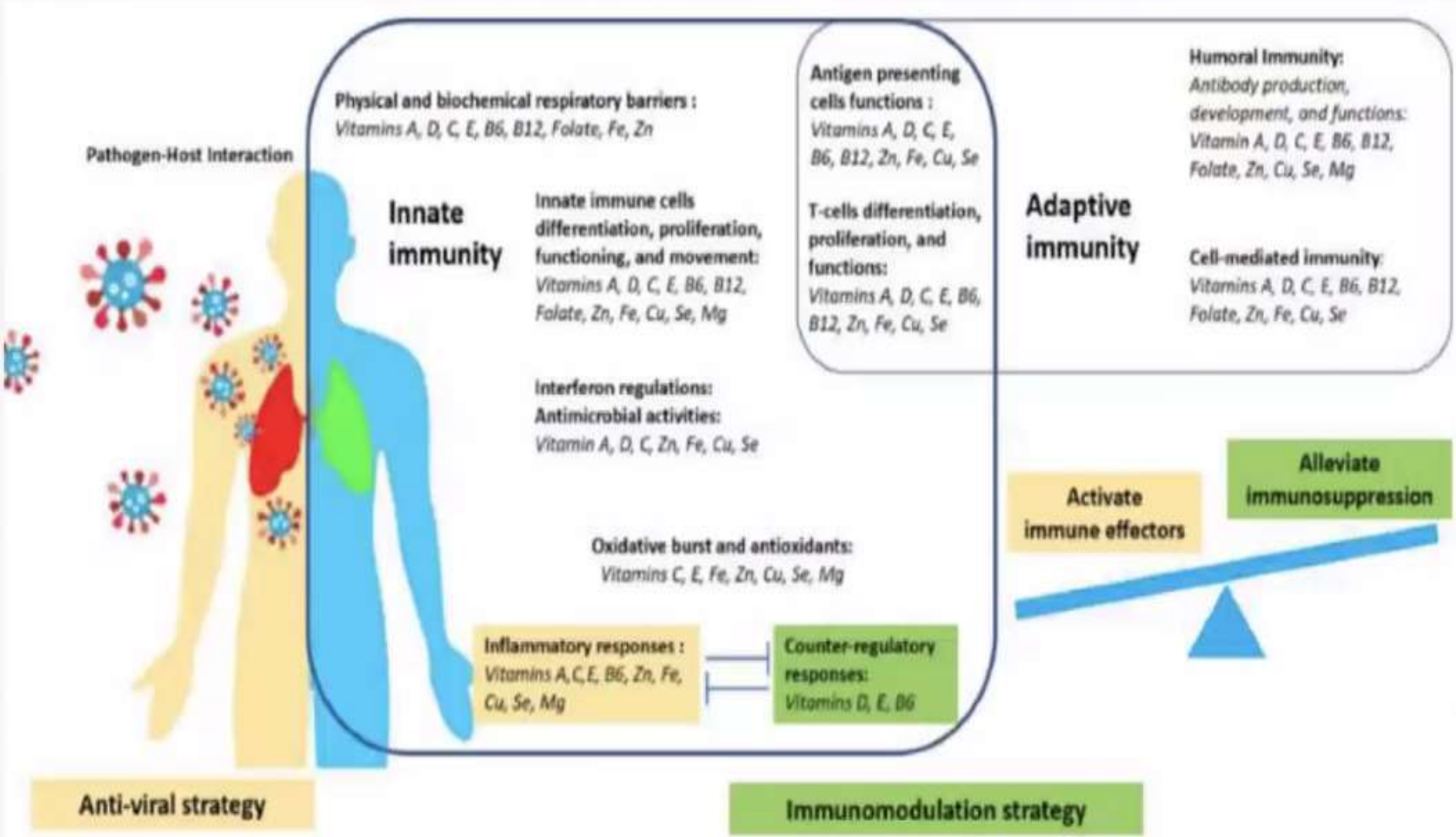


Fig. 1. The immunomodulation strategy and roles of a group of nutrients in different processes of virus-host immune responses.

IMMUNOSTIMULAN

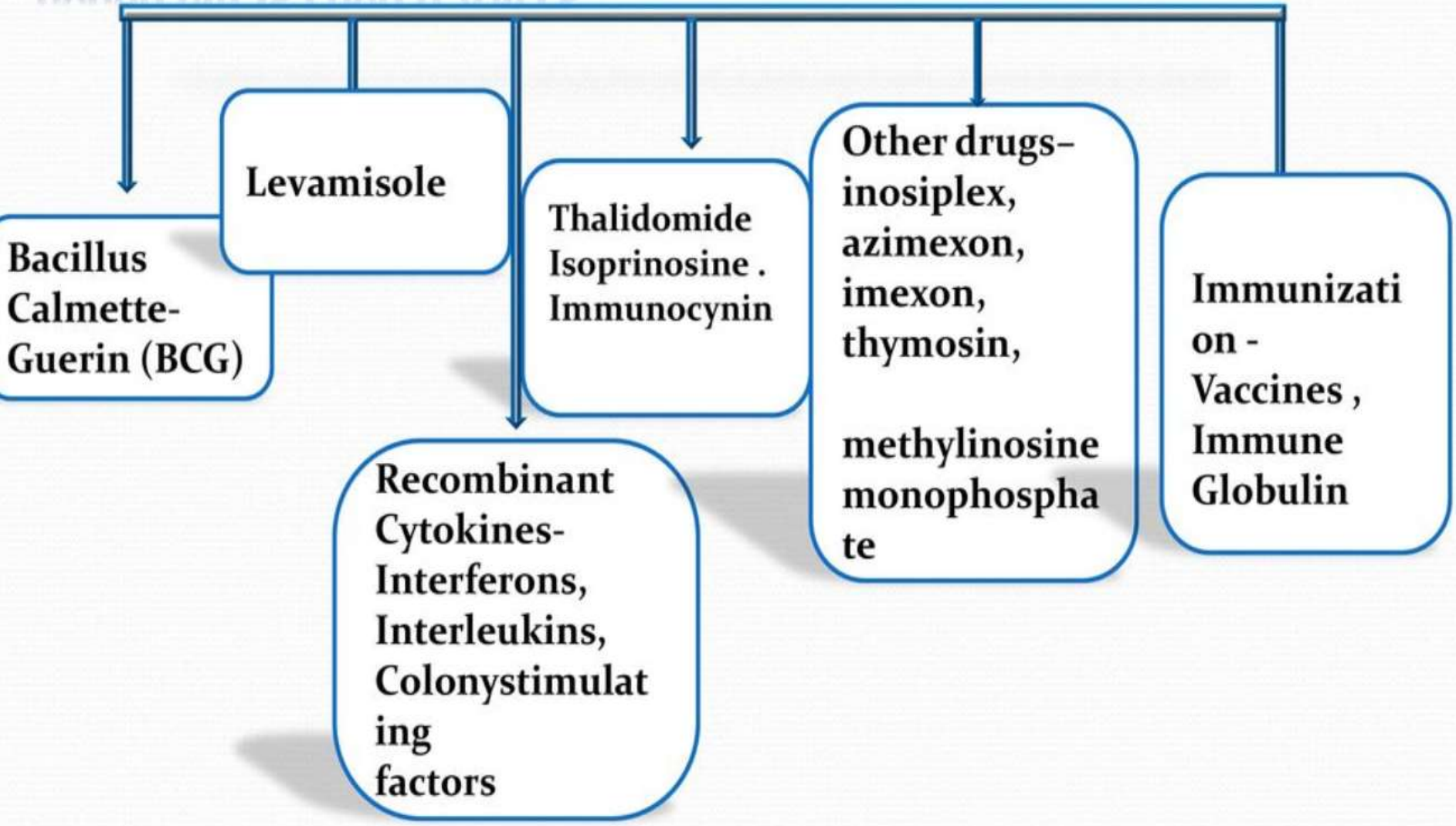
- Penggunaan :

1. Immunodeficiency disorder
2. Infeksi kronik
3. kanker

Immunostimulants (specific)

FAMILY	DRUG	PHARMACOLOGICAL EFFECT
Bacterial and fungal products	Bacillus Calmette-Guérin (BCG)	Activation of macrophages (APC), NK cells, and B lymphocytes
	Muramyl dipeptide (MDP) L-MTP-PE	Activation of macrophages (APC and phagocytosis) Activation of macrophages (APC and phagocytosis)
	Lipopolysaccharides (LPS)	Activation of macrophages and B lymphocytes
	Propionibacterium species	APC, phagocytosis, Activation of Tc and B lymphocytes
	Glucan	Phagocytosis
Thymic factors	Thymosins	Maturation of thymocytes into T lymphocytes
Synthetic drugs	Levamisole Isoprinosine	Maturation and activation of T lymphocytes, phagocytosis, and chemotaxis Proliferation of T lymphocytes; activation of Th, Tc, NK, phagocytosis and chemotaxis
Polyclonal antibodies	Specific antibodies	Triggering effector phase of specific immunity against various antigens
Recombinant cytokines	Interleukin 2 (IL-2)	Activation of lymphocytes Th (proliferation),
	Interleukin 1 (IL-1)	Tc (lysis), and B
	Interleukin 12 (IL-12)	Activation of Th lymphocytes
	Interferon gamma (IFN-γ)	Proliferation of monocytes Activation of macrophages, lymphocytes, and NK cells, increase in expression of MHC II
Monoclonal antibodies	Specific antibodies	Triggering effector phase of specific immunity against antigen (e.g., tumor)
Vaccines	Antigens	Triggering of specific immunity (phases of recognition, activation, and effector)

IMMUNOSTIMULANTS



BCG

Live, attenuated culture of BCG strain of Mycobacterium Bovis

MOA

Induction of a granulomatous reaction at the site of administration. It causes activation of macrophages to make them more effective killer cells

Therapeutic uses

Treatment and prophylaxis of carcinoma of the urinary bladder, Prophylaxis of primary and recurrent stage of papillary tumors after transurethral resection.

Adverse effects

Hypersensitivity, shock, chills, fever, malaise, and immune complex disease.

Levamizol / Ergamisol

- synthesized originally as an anthelmintic
- but appears to restore depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages

Therapeutic uses:

- Adjuvant therapy with 5-fluorouracil colon cancer, agranulocytosis.
- Used to treat immunodeficiency associated with Hodgkins disease

Adverse effects :

- Flu-like symptoms,
- allergic manifestation,
- nausea and
- muscle pain .

Thalidomide

- Severe, refractory rheumatoid arthritis .
- Multiple myeloma
- Adverse effects : Teratogenicity

- Enhanced T-cell production of cytokines – IL-2, IFN-γ
- NK cell-mediated cytotoxicity against tumor cells.
- Decrease circulating TNF-α in patients with erythema nodosum leprosum, but increase in HIV-seropositive patients,
- It affects angiogenesis also.

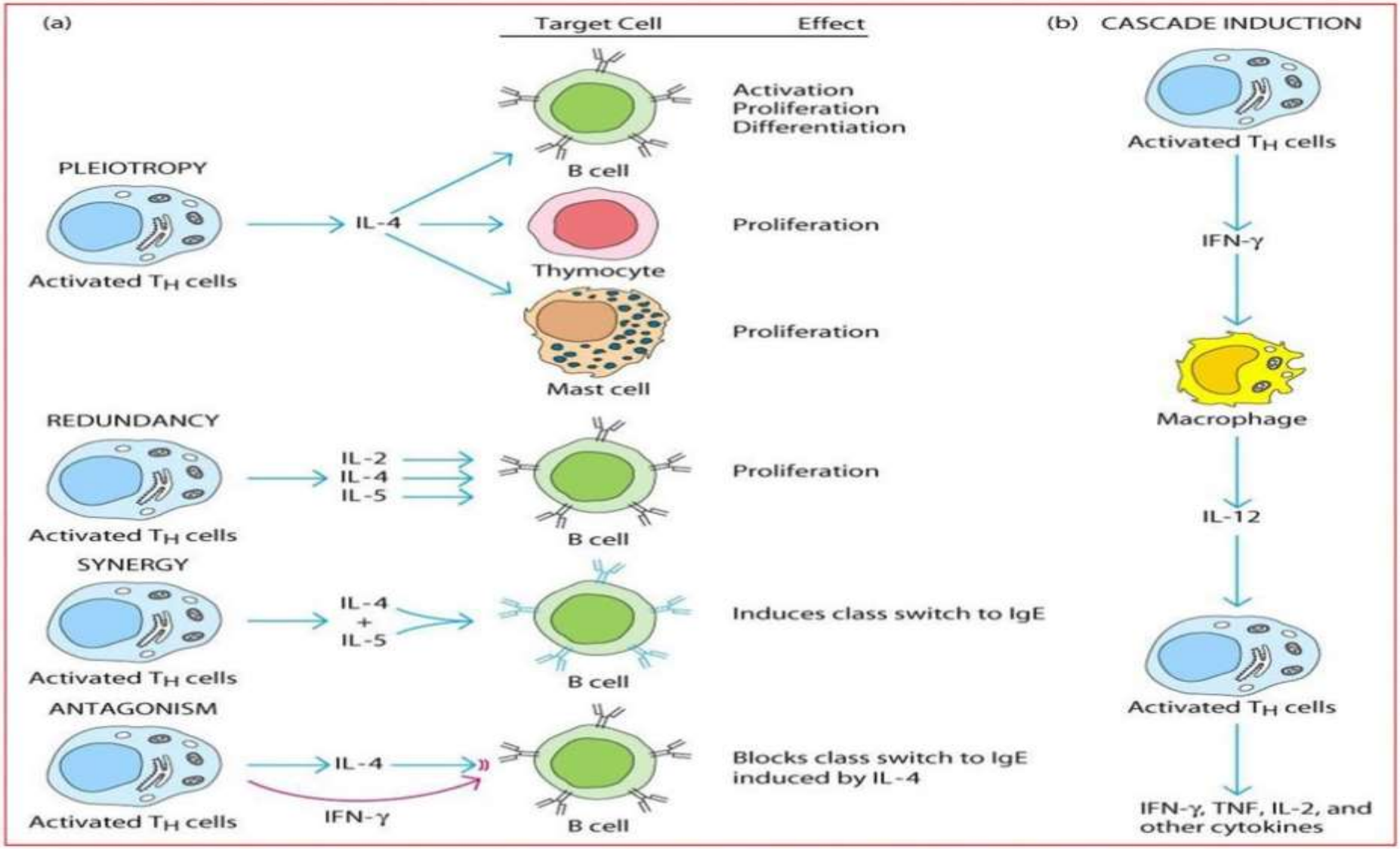
Penggunaan

Mekanisme Kerja

Recombinant Cytokines

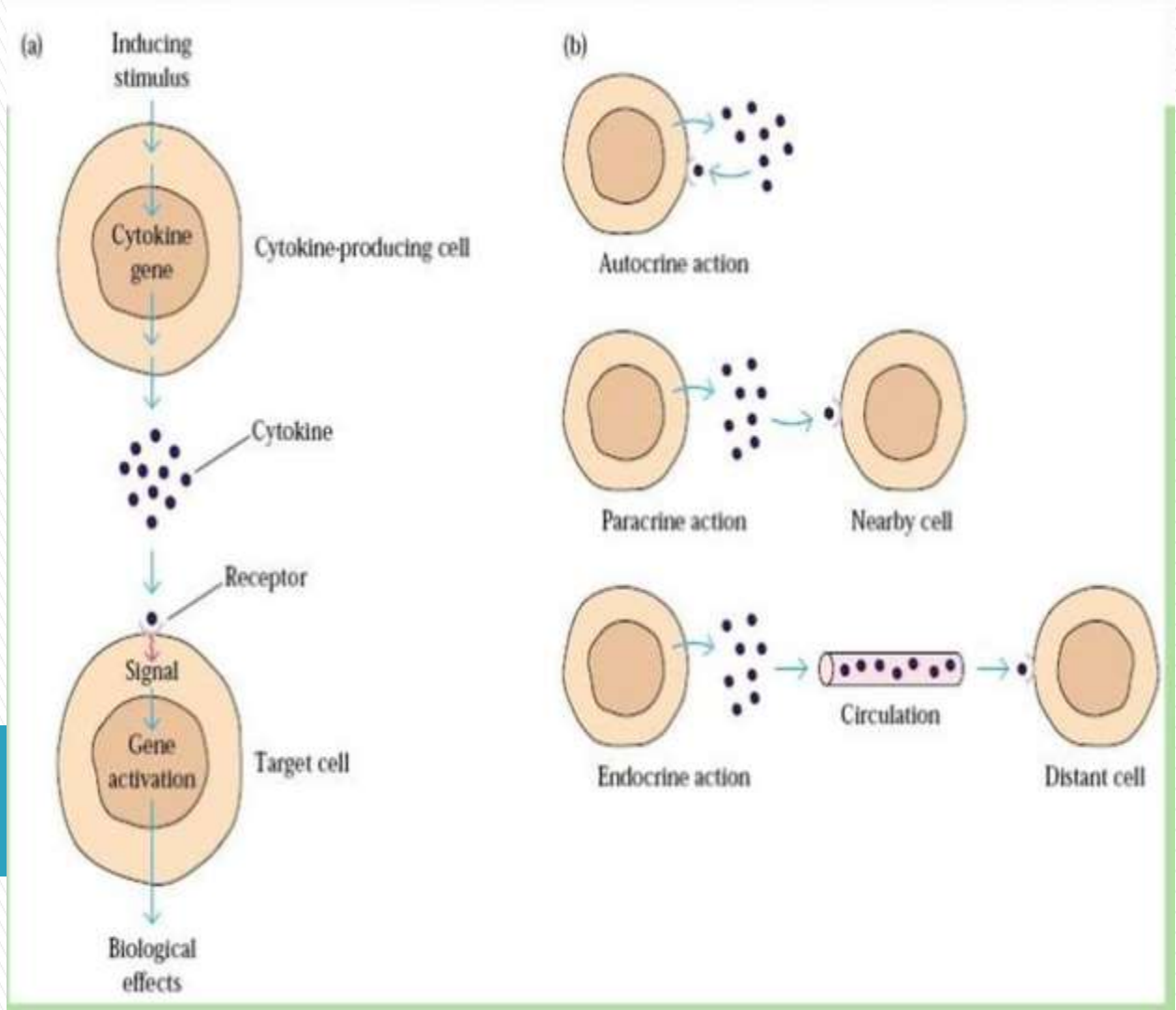
- Hormone like, small low molecular weight polypeptides.
- Maintain communication among cells to co-ordinate immune response. Act synergistically or antagonistically thereby enhancing or supressing their own production Autocrine, paracrine or endocrine in action.
- Causes tissue repair and provide resistance to infection

Cytokines : Properties



Cytokines : Action

- Autocrine
- Paracrine
- endocrine



NAME	SOURCE	FUNCTION	THERAPEUTIC AGENT
IL-1	Monocyte, lymphocyte, endothelium	Hematopoesis, co-stimulation of T cell, fibroblast proliferation, acute phase response	Blockage of IL-1 activity
IL-2	Activated T cell	T cell proliferation and differentaiation, B cell proliferation and Ig secretion, proliferation and cytolytic activity	Treatment of cancer & infectious diseases, bone marrow transplantation
IL-3	Activated T cell, mast cell, NK cell	Proliferation & differentiation of myeloid progenitor stem cell, prevention of apoptosis induction in macrophages	Bone marrow transplantation
IL-4	T cell, mast cell, eosinophil, basophil	B cell proliferation and differentaiation, Ig switching,	Antitumor agent, immune stimulator
IL-6	T cell, monocyte, endothelial cells, mast cells	Stimulate B cell for antibody production & T cell growth	Antitumor
IL-8	Monocyte, lymphocyte, endothelial cells	Neutrophil chemotaxis & activation, chemokine function	None
IL-10	Monocyte, lymphocyte, endothelial cells	Inhibition of proinflamatory cytokines by monocyte, granulocytes, inhibition of IL-2 production by T cell, inhibition of antigen specific T cell activation	Antiinflamatory & immunosupressive. used in autoimmune disease
IL-12	Monocyte, Bcells	Proliferation of T & NK cell, CTL response to tumor cell, ↑ IFN γ production by T & NK cell, inhibit Ig E production	Antimetastatic, antitumor, vaccine adjuvant
IL-13	Activated T , B cell	Bcell growth & differentaiation factor, stimulate chemotaxis	Antitumor,anti inflammatory agent

NAME	SOURCE	FUNCTION	THERAPEUTIC AGENT
IFN-α	Leucocyte	Antiproliferative action, immunoregulatory action	Cancers, hepatitis B, hepatitis C, AIDS, Kaposi sarcoma, multiple sclerosis
IFN-β	Fibroblast, epithelial cell, endothelial cell	Antiviral, MHC antigen upregulation, NK cell enhanced cytotoxicity, antimicrobial	Cancer, multiple sclerosis
IFN-γ	Monocyte, macophage, dendritic cell, T cell, B cell	MHC class II expression, macrophage & NK cell activation, Ig isotype selection	Infection with *Leishmania* & *Toxoplasma*. Used as adjuvant
G-CSF	Stromal cell, endothelial cell, fibroblast	Proliferation & differentiation of macrophage progenitor cell, emergency granulopoesis	After bone marrow transplantation
M-CSF	Fibroblast, endothelial cell, T cell, monocyte, neutrophil	Monocyte proliferation, differentiation & activation	Antitumor, anti-infection, myelo-supression
GM-CSF	T cell, macrophage, endothelial cell, B cell	Inhibit apoptosis of taget, proliferation , differentiation & activation of granulocyte, macophage lineage	Recruitment of peripheral blood stem cell, stimulation of APC for immunotherapy,

NAME	SOURCE	FUNCTION	THERAPEUTIC AGENT
α chemokines	Monocyte, neutrophil, endothelial cell, epithelial cell	Neutrophil chemotaxis & adherence, IL-6 secretion	None yet
β chemokines	Monocyte, fibroblast, epithelial cells, melanocytes	Monocyte activation, basophil activation, T cell chemotaxis, NK cel cytolysis	None yet
RANTES	T cell monocyte, NK cell, Fibroblast, epithelial cell, Endothelial cell	T cell chemotaxis & proliferation, monocytic chemotaxis & activation, NK cell chemotaxis, modulation of macrophages, eosinophils, T cells	Supression of HIV replication
TNF-α	Macrophages, T cell	Cytotoxic for tumor cell, antiviral, antibacterial, antiparasitic activity, growth stimulation, immunomodulation	Cancer & autoimmune disease
TNF-β	Mast cell, platelet, fibroblast	Wound repair, cell growth regulation, tissue remodelling, immunosupression,	Inhibition of inflammatory cell, treatment of breast cancer.

Cytokines-based Tx

S.N.	AGENT	NATURE	APPLICATION
1.	Enbrel	Chimeric TNF-receptors	Rheumatoid Arthritis
2.	Remicade/Humira	Mab against TNF-α receptors	Rheumatoid arthritis, cronh's dis.
3.	Roferon	INF-α	Hepatitis B ,kaposi's sarcoma, Feline leukemia
4.	Avonex	INF -β	Multiple sclerosis
5.	Actimmune	INF-γ	CGD, Osteopetrosis
6.	Neupogen	G-CSF	Increase Nphils,reduce Infection in Cancer&AIDS Patients
7.	Epogen	Erythropoietin	Increase RBC Production

Keterbatasan

- Maintain effective dose at local level.
- Repeated administration may be required.
- Can cause unpredictable and undesirable side
- effects. Fever, diarrhea, anaemia, shock etc.

Isoprinosine(Inosiplex)

- complex of the pacetamidobenzoate salt of N,N-dimethylamino-2- propanol: inosine in a 3:1 molar ratio

- augment production of cytokines such as IL-1, IL-2 and IFN-γ ,
- increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli,
- increases active T-cell rosettes and
- induces T-cell surface markers on prothymocytes

Mekanisme Kerja

Penggunaan

- Herpes simplex infections,
- subacute sclerosing panencephalitis,
- acute viral encephalitis caused by herpes simplex,
- Epstein-Barr and measles viruses

Adverse Effect

- Minor CNS depressant,
- transient nausea and
- rise of uric acid in serum and urine

Immunocynin

- stable form of haemocynin, a non-haeme, oxygen carrying,
- copper-containing protein found in arthropods and molluses

- Therapeutic uses:Urinary bladder cancer.
- Adverse effects:Rare-mild fever

IMMUNIZATION

- Administration of antigen as a whole, killed organism, or a specific protein or peptide constituent of an organism
- Booster doses
- Anticancer vaccines:
  - Vaccinating patients with autologous antigen presenting cells (APC) expressing tumor-associated antigens (TAA)

Indications

- Individual is deficient in antibodies – immunodeficiency
- Individual is exposed to an agent, inadequate time for active immunization
- Rabies
- Hepatitis B

Active immunization

Passive – Preformed antibody

IMMUNOSUPRESSAN

Penggunaan :

- Mengurangi kemampuan tubuh menolak organ transplantasi
- Menekan respon imun yang berlebihan

Klasifikasi :

- 1. selective inhibitor of cytokine production
- 2. immunosuppressive metabolite
- 3. antibodies
- 4. adrenocorticoid

Immunosupressan

SELECTIVE INHIBITORS OF CYTOKINE PRODUCTION AND FUNCTION

- *Cyclosporine*
- *Sirolimus*
- *Tacrolimus (FK506)*

IMMUNOSUPPRESSIVE ANTIMETABOLITES

- *Azathioprine*
- *Mycophenolate mofetil*
- *Mycophenolate sodium* (enteric coated)

ANTIBODIES

- *Alemtuzumab*
- Antithymocyte globulins
- *Basiliximab*
- *Daclizumab*
- *Muromonab-CD3 (OKT3)*

ADRENOCORTICOIDS

- *Methylprednisolone*
- *Prednisolone*
- *Prednisone*

IMMUNOSUPRESSAN

FAMILY	DRUG	PHARMACOLOGICAL EFFECT
Drugs that bind to immunophilins	Cyclosporine A, Tacrolimus and Sirolimus	Inhibition gene transcription of cytokines (e.g., IL-2) in T lymphocytes (blocking their proliferation), Inhibition of cytokines of T lymphocytes
Glucocorticoids	Prednisone and dexamethasone	Inhibition of transcription of cytokines into T lymphocytes and macrophages
Cytostatics	Azathioprine, Cyclophosphamide, Mophetil mycophenolate and Leflunomide	Inhibition of cell proliferation, Inhibition of proliferation of T and B lymphocytes, Inhibition of cell proliferation
Antilymphocyte antibodies	Polyclonal antibodies Anti-thymocytes	Triggering effector phase of specific immunity against lymphocytes
Monoclonal antibodies	Muromonab (OKT3) Anti-cytokines and anti-receptors	Destruction of CD3+ cells (T lymphocytes),Neutralization or destruction of molecules of the immune system
Hyposensitization	Allergens	Reversal of response from type IgE to IgC (from Th2 to Th1), Reduction in reactivity to allergen

Side Effects :

Immunodeficiency related with the increase susceptibility of (co)infections, some with septicemia Others: hypertension, dyslipidemia, hyperglycemia, peptic ulcers, lipodystrophy, liver & kidney injury Interaction with other medicine that affects the metabolism and action

Martinez AB, Mattila R, Gomez-FontR, Meurman JH. Immunomodulatory drugs : Oral and systemic adverse effects. Med Oral Patol Oral Cir Bucal 2014;1

Selective inhibitor of cytokine production

Exp : Cyclosporine, everolimus, sirolimus, tacrolimus

Cytokines are soluble, Antigen Non specific, signaling proteins that bind to cell surface receptors on a variety of cells.

The term cytokines includes the molecules known as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors and colony stimulating factors.

Siklosporin

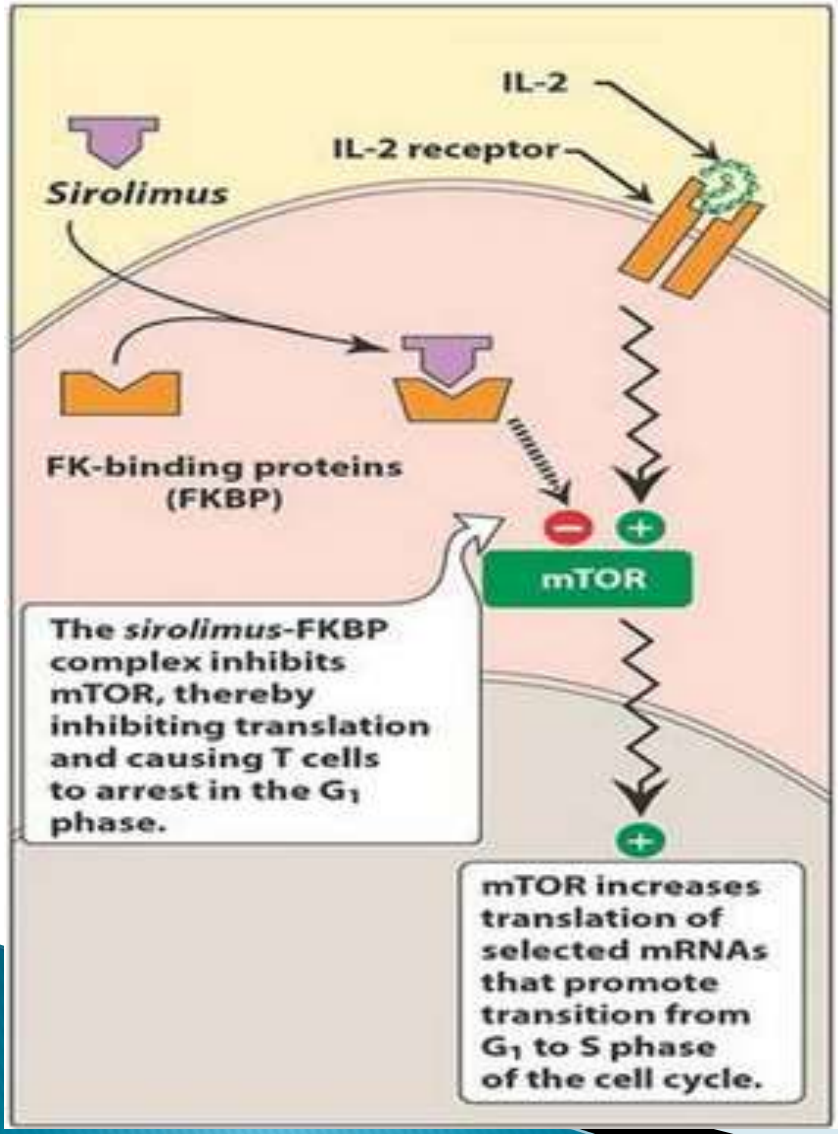
- merupakan peptida siklik nonribosomal yang terdiri atas 11 asam amino, dan diasingkan (isolasi) dari jamur tanah *Tolypocladium inflatum Gams* yang berasal dari Norwegia (Januari 1972).
- MOA = *Ciclosporin* berikatan dengan protein sitosolik *cyclophilin* (*imunophilin*) di limfosit, terutama limfosit T. Kompleks *ciclosporin* dan *cyclophilin* akan menghambat *calcineurin* yang dalam keadaan normal bertanggung jawab atas transkripsi IL-2.
- Di samping itu juga menghambat sintesis serta sekresi sitokin (interleukin), sehingga secara keseluruhan menghambat fungsi efektor limfosit T.

Tacrolimus

- berasal dari jamur tanah yang produksi oleh bakteri *Streptococcus tsukubaensis*, oleh karenanya juga dikenal sebagai '*Tsukuba macrolide immunosuppressant*' atau FK-506.

- MOA = mengurangi kegiatan (aktivitas) enzim *peptidyl-prolyl isomerase* dengan cara mengikat FKBP12 (FK506-protein pengikat/binding protein) membentuk kompleks baru FKBP12-FK506 dan selanjutnya interaksi dan menghambat *calcineurin*, jadi menghambat transduksi isyarat (signal) limfosit T dan transkripsi IL-2.

Sirolimus dan Tacrolimus



SIROLIMUS AND TACROLIMUS bind to the same cytoplasmic FK-binding protein, but instead of forming a complex with calcineurin, SRL binds to molecular target of rapamycin interfering with Signal.

The latter is a serine-threoninekinase Binding of **SIROLIMUS** to molecular target of rapamycin blocks the progression of activated T cells from the G_1 to the S phase of the cell cycle and, consequently, the proliferation of these cells.

Unlike Cyclosporine and Sirolimus and Tacrolimus does not owe its effect to lowering IL-2 production but, rather, to inhibiting the cellular responses to IL-2.

Immunosuppressive antimetabolites

- Azathioprine
- Mycophenolate mofetil
- Mycophenolate sodium

These agents are generally used in combination with corticosteroids and calcineurin inhibitors, cyclosporine and Tacrolimus.

Azathioprine

- merupakan turunan (derivat) merkaptopurin
- MOA = menghambat sintesis purin yang diperlukan dalam proliferasi sel, terutama leukosit dan limfosit.

Antibodies

- Alemtuzumab
- Antithymocyte globulins
- Basiliximab
- Daclizumab
- Muromonab-CD3

Alemtuzumab

It exerts its effects by causing profound depletion of T cells from the peripheral circulation.

Antithymocyte globulins

Thymocytes are developed in thymus and serve as precursors. The antibodies bind tp the surface of circulating T lymphocytes, which then undergoes complement mediated destruction, Ab. Depending cytotoxicity, apoptosis and opsonization. The Ab. Bound cells are phagocytosed in the liver and spleen, resulting in lymphopenia and impaired T-cell responses.

IL-2 receptor antagonist

- Basiliximab
- Daclizumab

Mechanism of action

Both compounds are anti-CD-2 antibodies and bind to the α chain of the IL-2 receptor on activated T-cells. They thus interfere with the proliferation of these cells. Basiliximab is 10 fold more potent than Daclizumab as a blocker of IL-2 stimulated T-cell replication. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

KORTIKOSTEROID

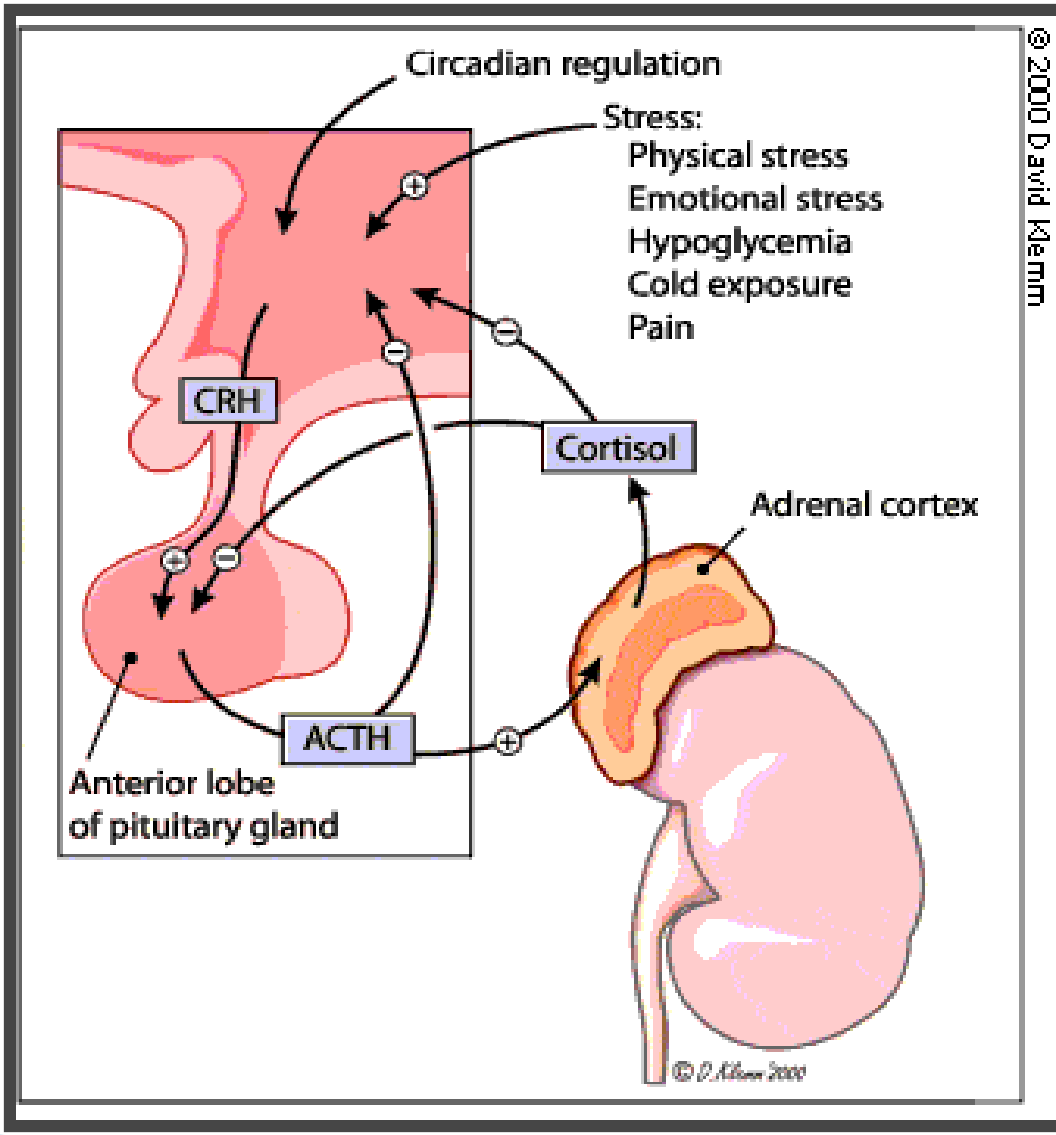
Methylprednisolone
Prednisolone
Prednisone

Hypothalamic-Pituitary Adrenal (HPA) Axis

Negative Feedback control of ACTH Production.

Suppression of HPA

STRESS: Overrides the neg. feedback mechanism.

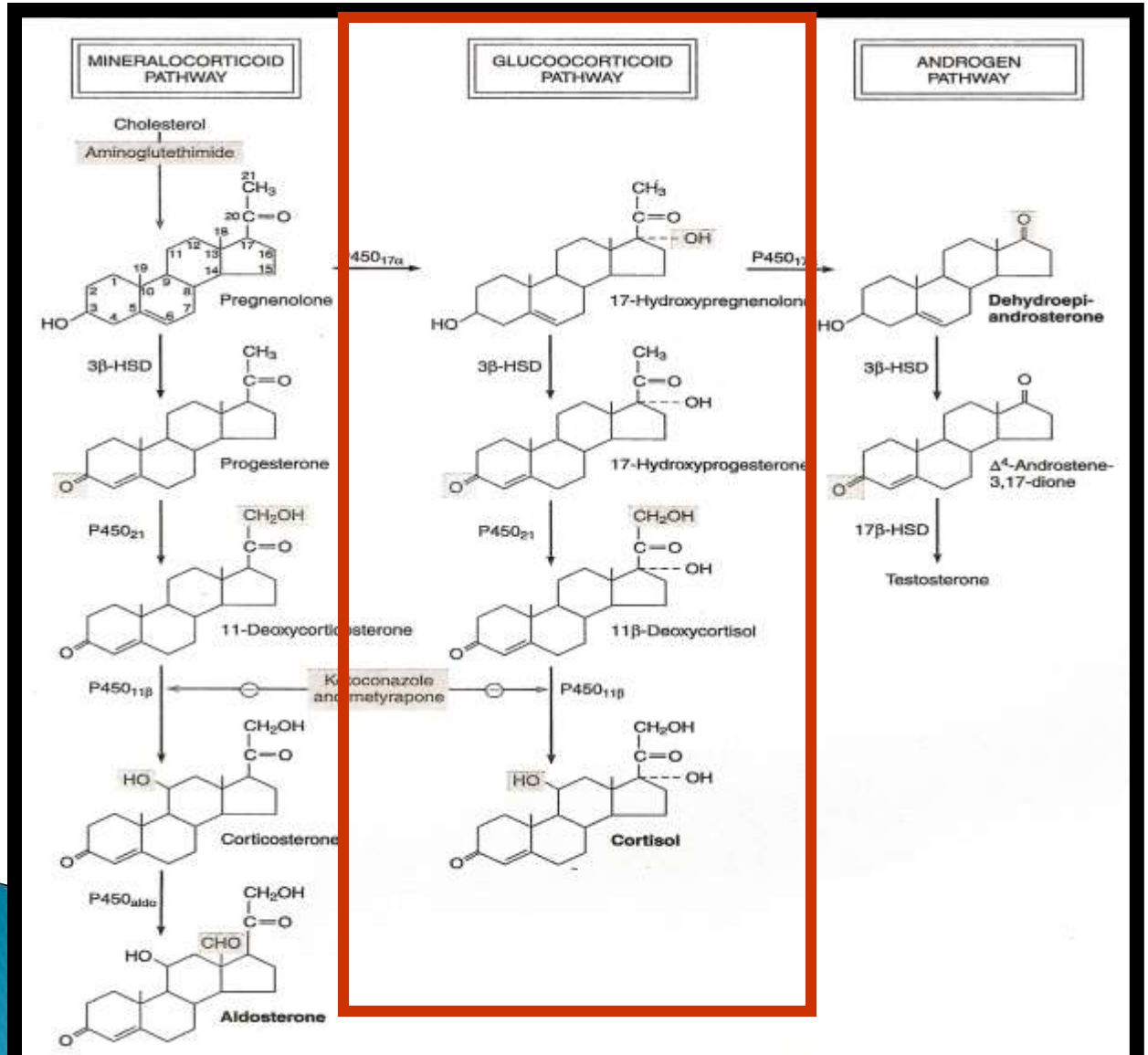


Adrenal cortex

Produces 30 steroid hormones

Major divisions include:
Glucocorticoids
Mineralocorticoids
Adrenal Sex steroids

Biosynthesis of Glucocorticoids (GCs)



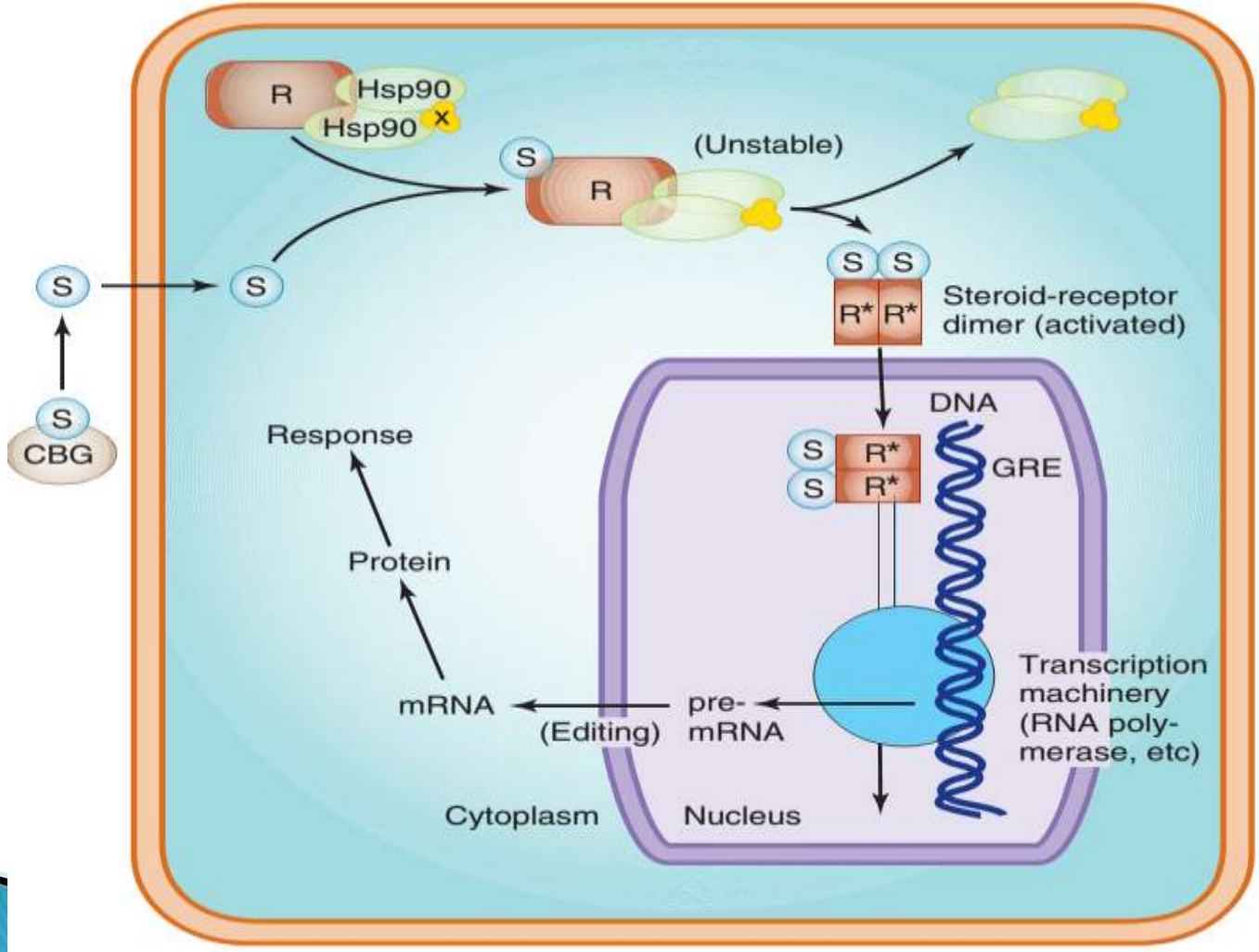
Glucocorticoids

Cortisol (95%)
Corticostrone
Cortisone

90% bound to plasma proteins

Circadian release Of GCs; highest in the early morning and lowest in the evening.

Aktivasi Reseptor Steroid



Aktivasi Reseptor Steroid

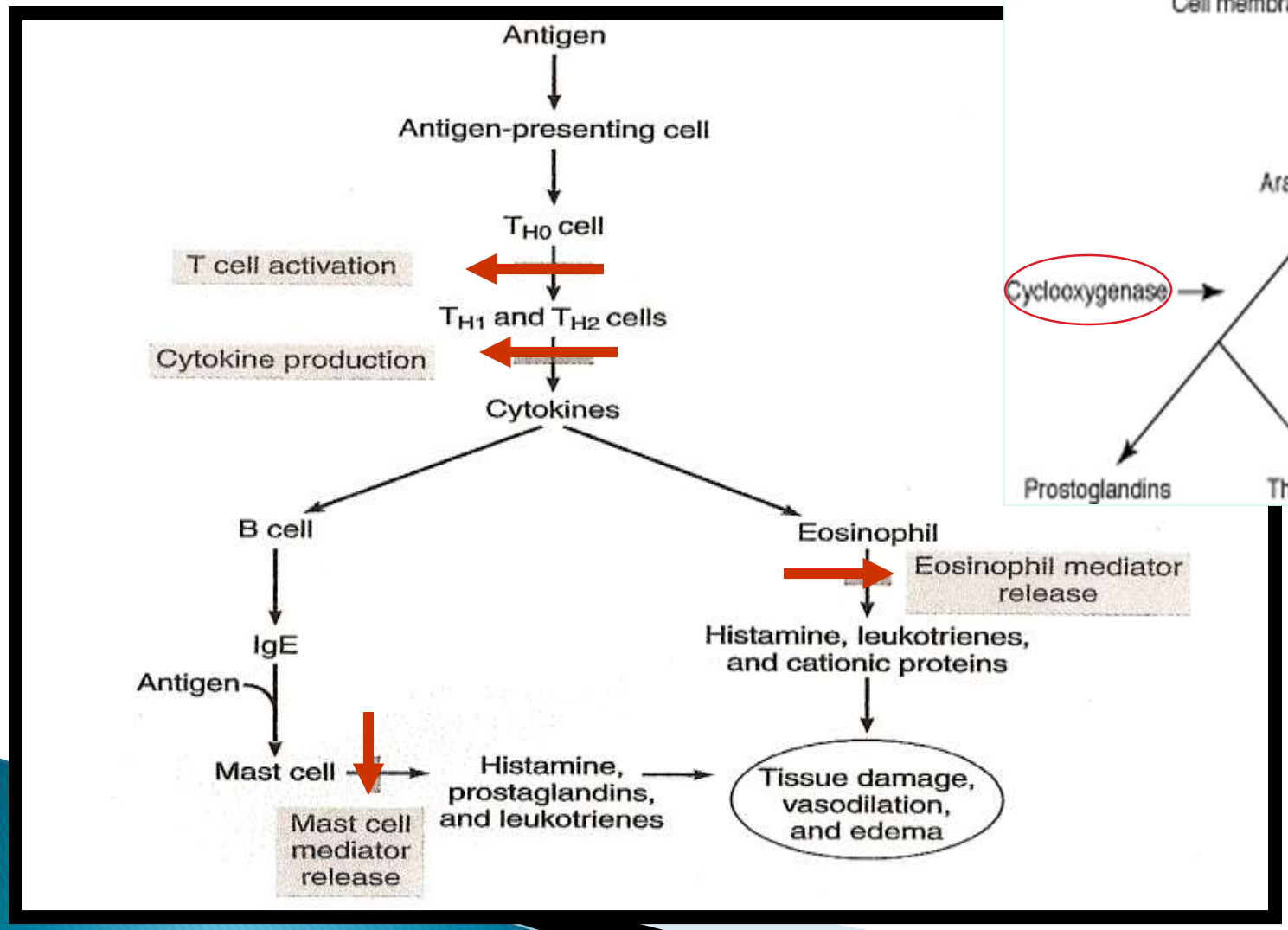
- S mengikat resept S(R) di sitoplasma, R sec normal berhub dg 2 molekul hsp90. kompleks S-R translokasi ke nukleus dan berinteraksi dg GRE (glucocorticosteroid response element) pd rantai promotor sel target → mempengaruhi proses transkripsi & sintesa protein

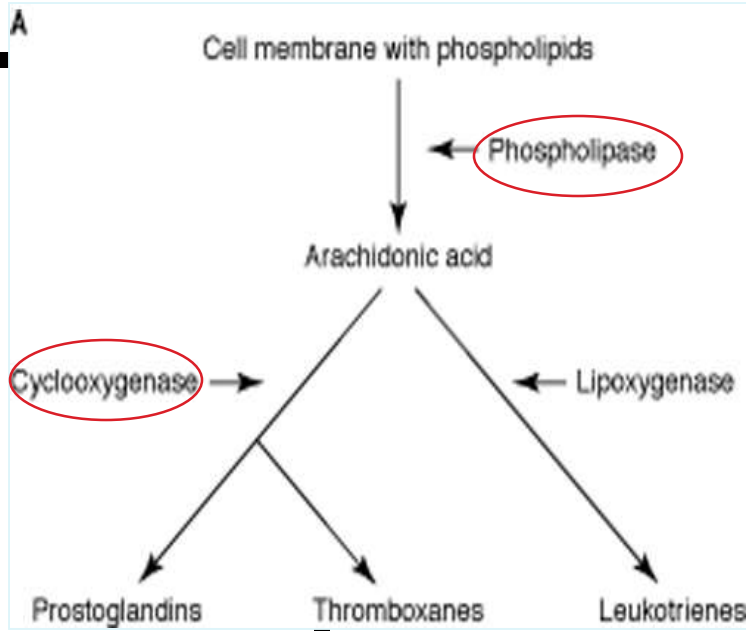
- Antara lain menyebabkan :
  - ✓ Induksi sintesa polipeptida (lipocortin-1) yg menghambat enzim fosfolipase A2 → menurunkan produksi mediator inflamasi (PG, leukotrien, platelet-activating factor /PAF)
  - ✓ Netralisasi peran transcription factor (mis. AP1) dlm sintesa sitokin (IL5, TNFα) → sintesa sitokin↓→ me ↓ inflamasi

FISIOLOGI KORTISOL

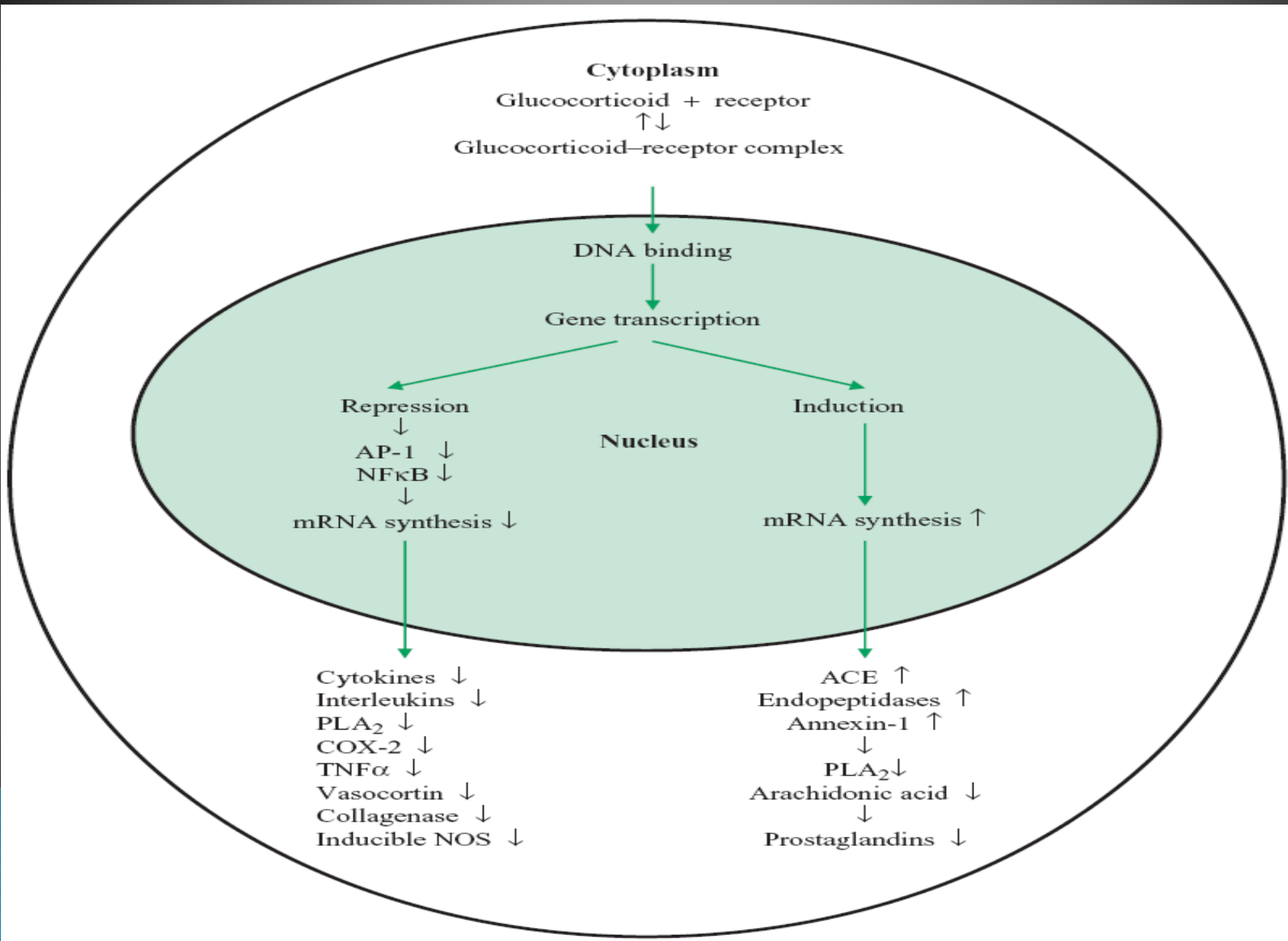
- Metabolic Effect
- **Anti-inflammatory effect**
- Antiproliferative effect
- **Immunosuppressive effect**

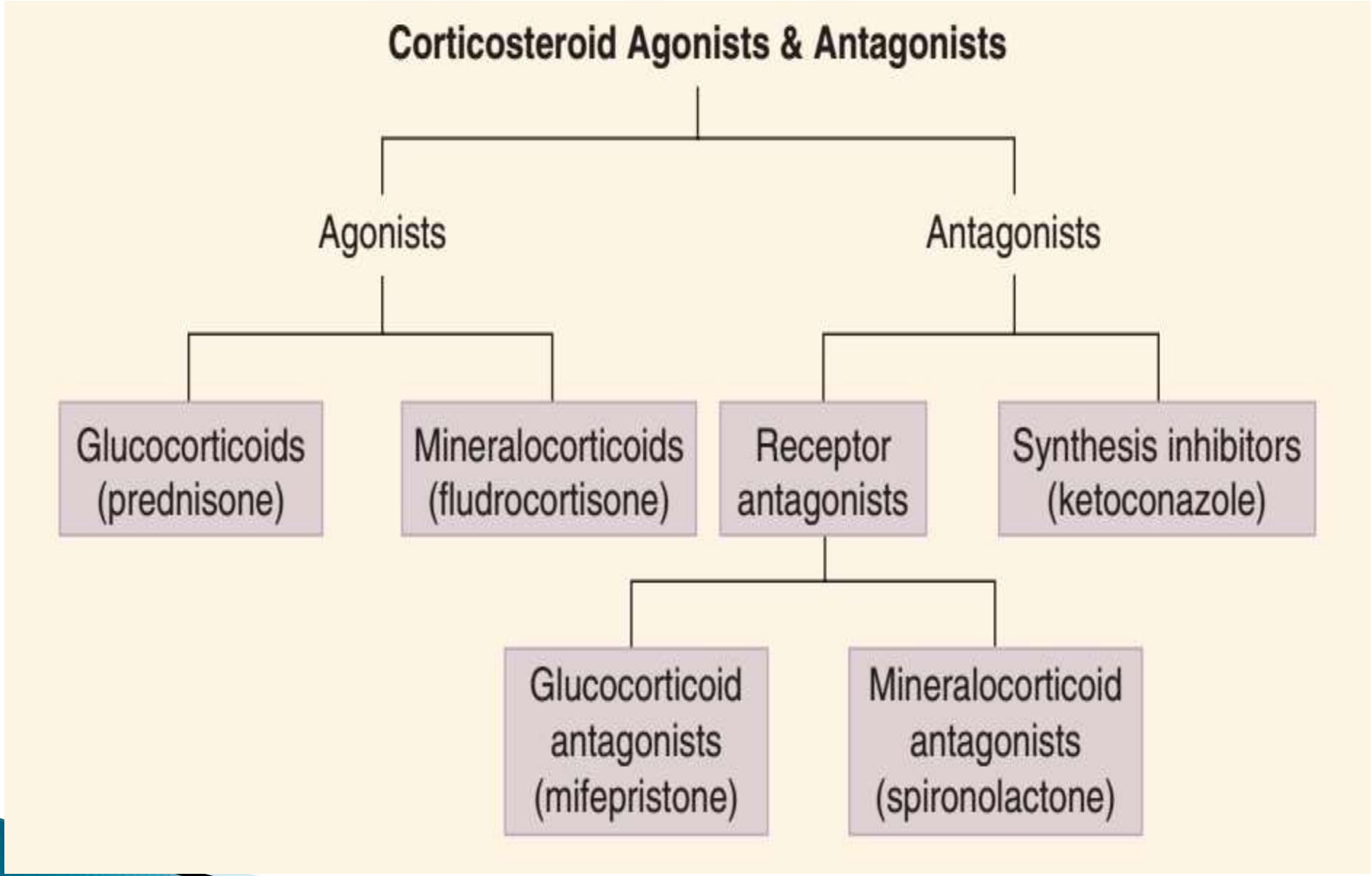
B. Mechanism of Action for Anti-Inflammatory Steroids





C. Mechanism of Action for Immunosupressive Steroids




Corticosteroid Agonists & Antagonists
Agonists
Antagonists
Glucocorticoids (prednisone)
Mineralocorticoids (fludrocortisone)
Receptor antagonists
Synthesis inhibitors (ketoconazole)
Glucocorticoid antagonists (mifepristone)
Mineralocorticoid antagonists (spironolactone)

Penggunaan Glukokortikoid

- Insufisiensi Adrenal
- Supresi HPA-axis overaktif
- Supresi penyakit autoimmun
- Mencegah rejeksi organ transplantasi
- Terapi limfosit-derived tumor
- Terapi penyakit allergi (asma, penyakit kulit allergi)

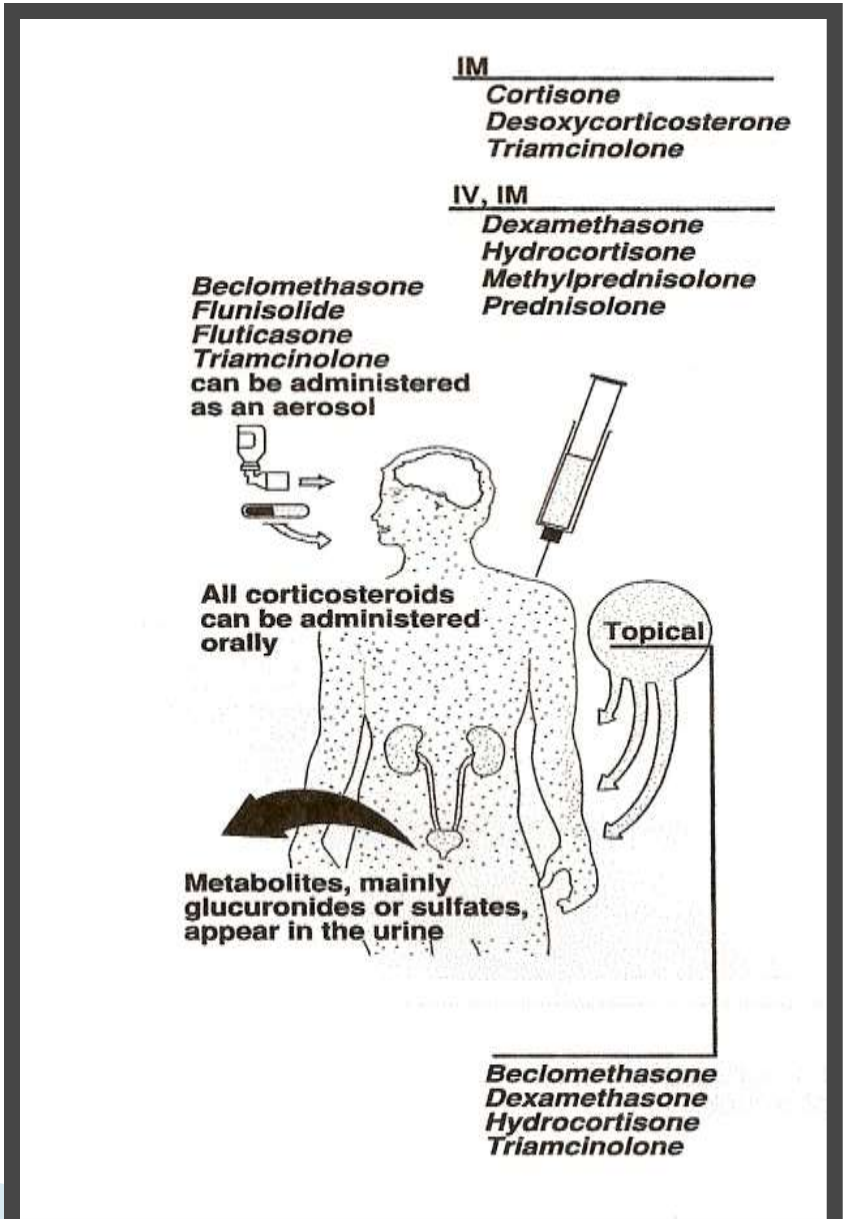
NONENDOCRINE DISORDERS TREATED WITH GLUCOCORTICOIDS

General Indication	Principal Desired of Glucocorticoids	Examples of Specific Disorders
Allergic disorders	Decreased inflammation	Anaphylactic reactions, drug-induced allergic reactions, severe hay fever, serum sickness
Collagen disorders	Immunosuppression	Acute rheumatic carditis, dermatomyositis, systemic lupus erythematosus
Dermatologic disorders	Decreased inflammation	Alopecia areata, dermatitis (various forms), keloids, lichens, mycosis fungoides, pemphigus, psoriasis
Gastrointestinal disorders	Decreased inflammation	Crohn disease, ulcerative colitis
Hematologic disorders	Immunosuppression	Autoimmune hemolytic anemia, congenital hypoplastic anemia, erythroblastopenia, thrombocytopenia
Nonrheumatic inflammation	Decreased inflammation	Bursitis, tenosynovitis
Neoplastic disease	Antilymphocytic effects	Leukemias, lymphomas, nasal polyps, cystic tumors
Neurologic disease	Decreased inflammation and immunosuppression	Tuberculous meningitis, multiple sclerosis, myasthenia gravis
Neurotrauma	Decreased edema;* inhibit free radical-induced neuronal damage	Brain surgery, closed head injury, certain brain tumors, spinal cord injury
Ophthalmic disorders	Decreased inflammation	Chorioretinitis, conjunctivitis, herpes zoster ophthalmicus, iridocyclitis, keratitis, optic neuritis
Organ transplant	Immunosuppression	Transplantation of liver, kidney, heart, and so forth
Renal diseases	Decreased inflammation	Nephrotic syndrome, membranous glomerulonephritis
Respiratory disorders	Decreased inflammation	Bronchial asthma, berylliosis, aspiration pneumonitis, symptomatic sarcoidosis, pulmonary tuberculosis
Rheumatic disorders	Decreased inflammation and immunosuppression	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, gouty arthritis, osteoarthritis

*Efficacy of glucocorticoid use in decreasing cerebral edema has not been conclusively proved.

Routes of Administration for GC

- Local (Preferred)
  - Intra-articular, IA
  - Intrabursal, IB
  - Intralesional, IL
  - Intrasynovial, IS
  - Soft tissue, ST
  - Intrarectal, IR
  - **Topical**
  - Nasal
  - **Inhaled**
- Systemic
  - **Oral, PO**
  - Intramuscular, IM
  - Intravenous, IV
  - Subcutaneous, SC



Glucocortikoid sistemik

Short-acting glucocorticoids

	Anti-inflammatory effect	Salt-retaining effect
Hydrocortisone	1	1
Cortisone	0.8	0.8

Intermediate-acting glucocorticoids

	Anti-inflammatory effect	Salt-retaining effect
Prednisone	4	0.3
Prednisolone	5	0.8
Methylprednisolone	5	0.5
Triamcinolone	5	0

Long-acting glucocorticoids

	Anti-inflammatory effect	Salt-retaining effect
Betamethasone	35	0
Dexamethasone	30	0
Paramethasone	10	0

Corticosteroids control symptoms and DO NOT stop progression (cure) of the disease

Glukokortikoid Sistemik

TABLE 26–9. Pharmacodynamic/Pharmacokinetic Comparison of the Corticosteroids

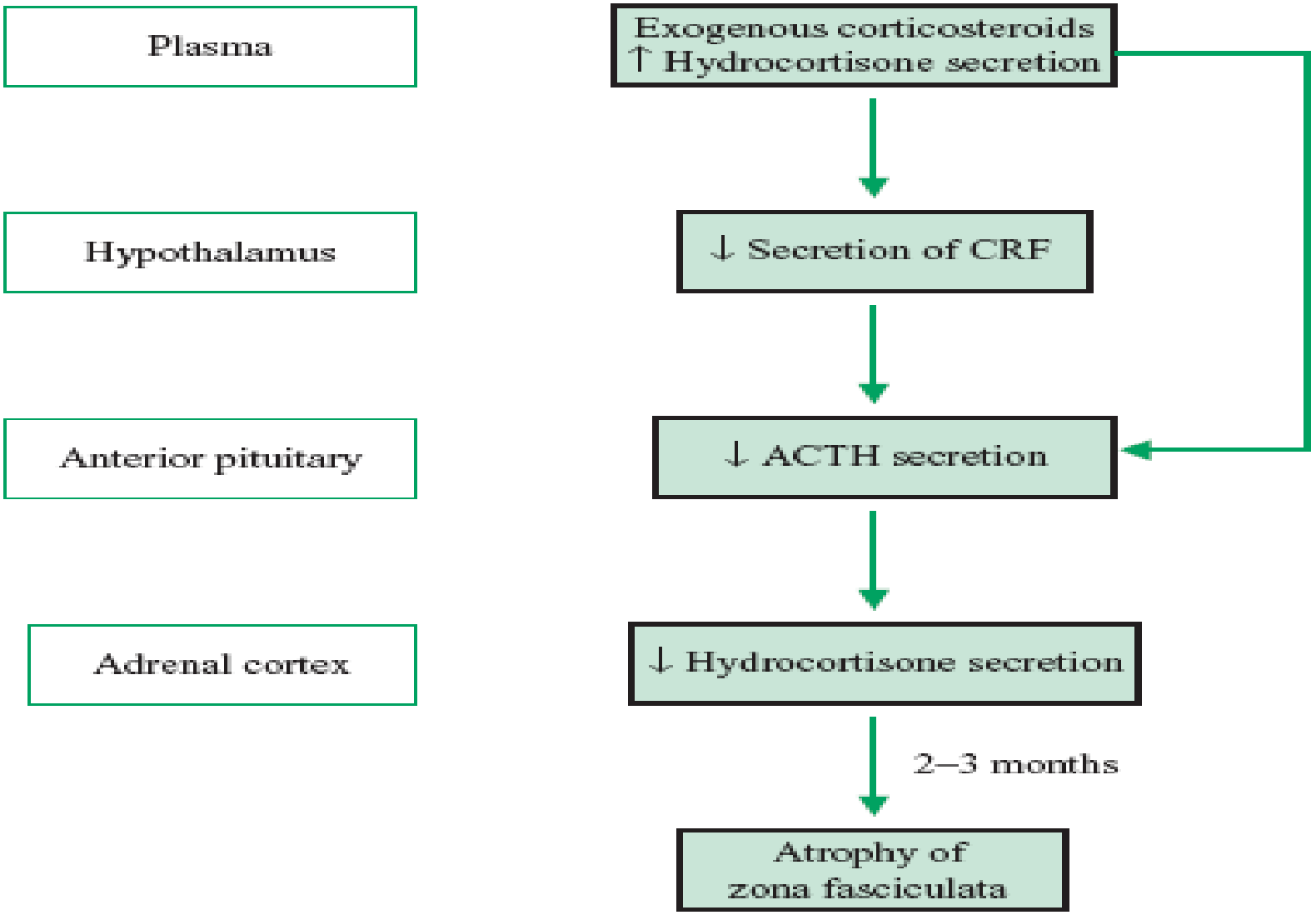
Systemic	Anti-inflammatory Potency	Mineralcorticoid Potency	Duration of Biologic Activity (h)	Elimination Half-Life (h)
Hydrocortisone	1	1.0	8–12	1.5–2.0
Prednisone	4	0.8	12–36	2.5–3.5
Methylprednisolone	5	0.5	12–36	3.3
Dexamethasone	25	0	36–54	3.4–4.0
Triamcinolone	5	0	18-36	3,0
Betamethasone	25	0	18-36	4,0

Farmakokinetik GC sistemik

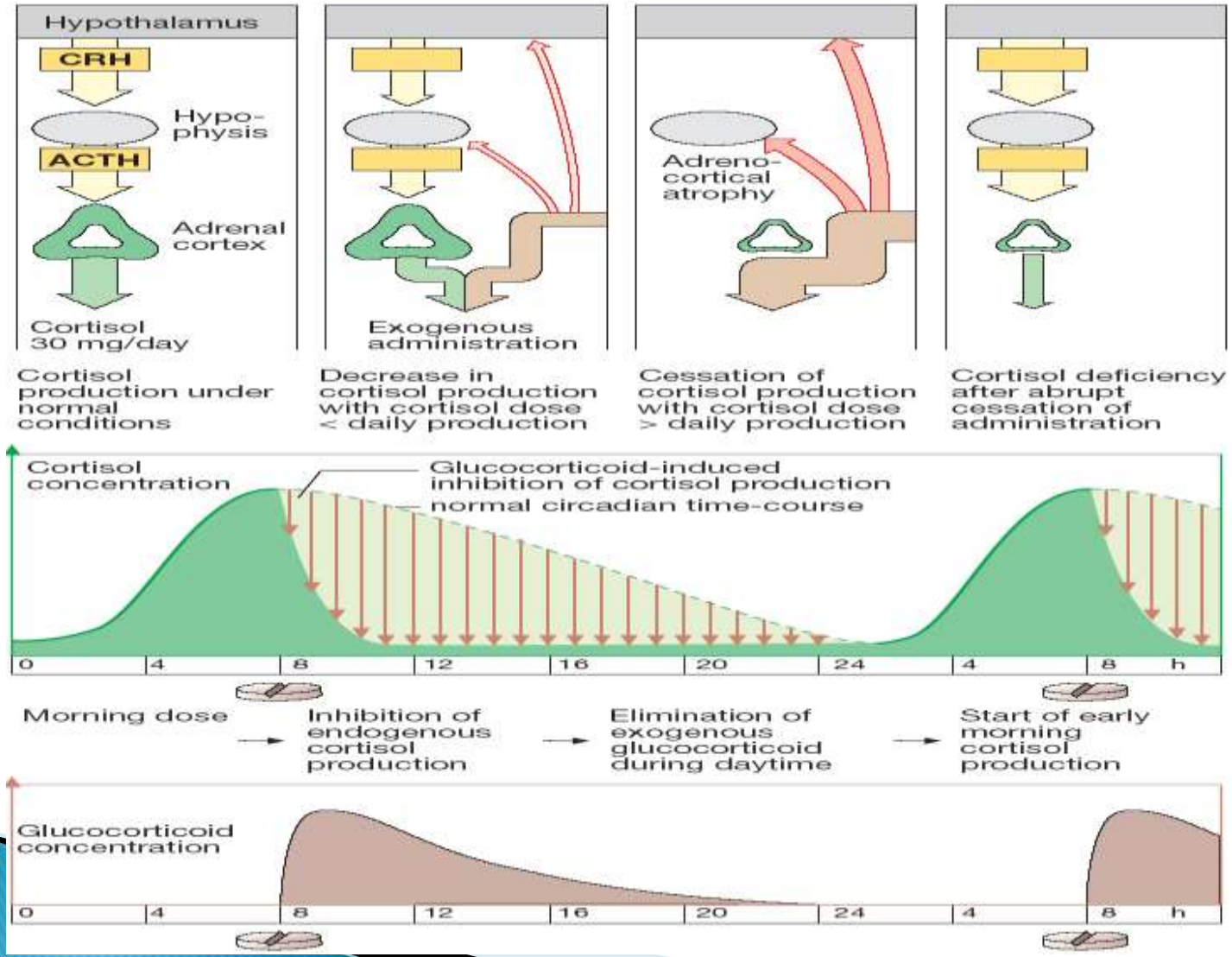
- Pemberian corticosteroids pd konsentrasi fisiologis selama minimal 2 minggu akan menekan HPA axis, shg terjadi penurunan 'endogenous hormones'. Recovery setelah 9-12 bulan.

- Metabolisme Hepar :
  - Hepar : tempat inaktivasi / metabolisme utama GC. GC dimetabolisme oleh enzim cytochrome P450 3A4
  - 25% GC diekskresi bersama empedu & feces.

- Renal Clearance
  - 75 % metabolit GC diekskresi bersama urine.


Plasma
Hypothalamus
Anterior pituitary
Adrenal cortex
Exogenous corticosteroids
↑ Hydrocortisone secretion
↓ Secretion of CRF
↓ ACTH secretion
↓ Hydrocortisone secretion
2–3 months
Atrophy of
zona fasciculata

Dampak Pemberian Glucocorticoid pada *Cortisol Release*



Inhaled Glucocorticoids:

"Long-term control" of Chronic Asthmatic Symptoms

Beclomethasone
Budesonide
Flunisolide
Fluticasone propionate
Triamcinolone acetonide

Taken Daily, over a long period of time

SE: oropharyngeal candidiasis (Thrush), dysphonia (hoarseness), adrenal suppression, bone loss, in children, retarded growth

Reduced risk of toxicity with inhaled preparations

Mechanisms of Action:

- Reduce bronchial hyperreactivity
- Decreased synthesis and release of inflammatory mediators, e.g, leukotrienes, prostaglandins and histamine
- Decreased infiltration and activity of inflammatory cells, e.g. eosinophils, leukocytes)
- Decreased edema of the airway mucosa and mucus production
- Increase responsiveness to β_2 agonists

Kortikosteroid Topikal

Topical steroid class American calssification	Topical steroid class Brithis classification	Common representative topical steroids	Indications
I Superpotent corticosteroids	I Very potent	Clobetasol propionate 0.05% cream or ointment	Alopecia areata
		Halobetasol propionate 0.05% cream or ointment	Atopic dermatitis (resistant)
		Betamethasone dipropionate 0.05% ointment	Discoid lupus
		Betamethasone dipropionate 0.05% cream	Hyperkeratotic eczema
II Potent corticosteroids	II Potent	Flucinonide 0.05% ointment	Lichen planus
		Halcinonide 0.1% cream	Lichen sclerosus (skin)
		Mometasone furoate 0.1% ointment	Lichen simplex chronicus
		Betamethasone dipropionate 0.05% lotion	Nummular eczema
III Upper mid-strength corticosteroids		Fluticasone propionate 0.005% ointment	Psoriasis
		Triamcinolone acetonide 0.1% ointment	Severe hand eczema
		Halometasone 0.05% cream	

Topical steroid class American calssification	Topical steroid class Brithis classification	Common representative topical steroids	Indications
IV Mid-strength corticosteroids		Flucinolone acetonide 0.025% ointment	Asteatotic eczema
		Mometasone furoate 0.1% cream or lotion	Atopic dermatitis
V Lower mid-strength corticosteroids	III Moderate	Betamethasone valerate 0.1% cream	Lichen sclerosus (vulva)
		Flucinolone acetonide 0.025% cream	Nummular eczema
		Fluticasone propionate 0.05% cream	Scables (after scabicide)
		Hydrocortisone butyrate 0.1% cream	Seborrheic dermatitis
			Severe dermatitis
			Severe intertrigo (short-term)
			Statis dermatitis
VI Mild corticosteroids		Alclometasone dipropionate 0.05% cream or onintment	Dermatitis (diaper)
		Desonide 0.05% cream	Dermatitis (eyelids)
		Fluocinolone acetonide 0.01% cream	Dermatitis (face)
		Triamcinolone acetonide 0.025% cream	Intertigo

Topical steroid class American calssification	Topical steroid class Brithis classification	Common representative topical steroids	Indications
VII Least potent corticosteroids	IV Mild	Hydrocortisone 1% or 2.5% cream, 1% or 2.5% lotion, 1% or 2.5% ointment	Perianal inflammation
		Hydrocortisone acetate (1% or 2.5% cream, 1% or 2.5% lotion, 1% or 2.5% ointment)	

Courtesy *Adapted from Ference JD, Last AR, Choosing topical corticosteroids, Am Fam Physician 2009;79:135-140

Prinsip Pemakaian Steroid Topikal

- Untuk sebagian besar obat sebaiknya diberikan 1 – 2 x/hari. Untuk daerah telapak tangan dan kaki dapat diberikan lebih sering.
- Panjang dari krim atau salep yang dikeluarkan dari tube dapat diukur dengan satuan FTU (Finger Tip Unit = 1 ruas jari telunjuk orang dewasa). Satu FTU (sekitar 500 mg) dapat dipakaikan 2 x ukuran tangan orang dewasa.
- Pemakaian selang – seling 1 hari direkomendasikan pada kondisi kronis.
- Kortikosteroid topikal potensi sangat tinggi hanya direkomendasikan untuk dipakai selama 1 – 2 minggu (paling lama 3 minggu) kemudian beralih ke potensi yang lebih ringan seiring dengan perbaikan kondisi.

2 FTU = 1 g

FTU = *Fingertip Unit* / 1 FTU = 0.5 g *of cream or ointment*

Tabel 3. Pedoman FTU untuk dewasa[14]

Guidlines for adults		
Anatomic area	**FTU required**	**Amount needed for twice daily regimen in g**
Face and neck	2.5	2.5
Anterior and posterior trunk	7	7
Arm	3	3
Hand (both sides)	1	1
Leg	6	6
Foot	2	2

Tabel 4. Pedoman FTU untuk anak-anak[15]

Guidlines for children				
Anatomic area	**FTU required**	**Amount needed for twice daily regimen in g**		
	3-6 months	**1-2 years**	**3-5 years**	**6-10 years**
Face and neck	1/1	1.5/1.5	1.5/1.5	2/2
Arm and hand	1/1	1.5/1.5	2/2	2.5/2.5
Leg and foot	1.5/1.5	2/2	3/3	4/4
Anterior trunk	1/1	2/2	3/3	3.5/3.5
Posterior trunk and Buttocks	1.5/1.5	3/3	3.5/3.5	5/5

	Topical corticosteroids (adverse effects)	
	Cutaneous	**Systemic**
Striae distensae	Milia	Hypothalamic-pituitary-adrenal axis suppression
Cutaneous atrophy	Masking fungal infection (tinea incognito), worsening of herpes, demodex, scabies, candidiasis	
Stellate pseudoscars		Cushing's disease
Telangiectasia		Femoral head osteonecrosis
Purpura		Cataracts
Erythema	Granuloma gluteale infantum	Glaucoma
Perioral dermatitis	Hypertrichosis	Decreased growth rate
Rosacea	Photosensitisation	Hyperglycemia
Acne	Hypopigmentation	Hypertension
Rebound erythema	Hyperpigmentation	Hypocalcemia
Steroid addiction	Contact dermatitis	Peripheral edema
Topical steroid dependent face	Tachyphylaxis	

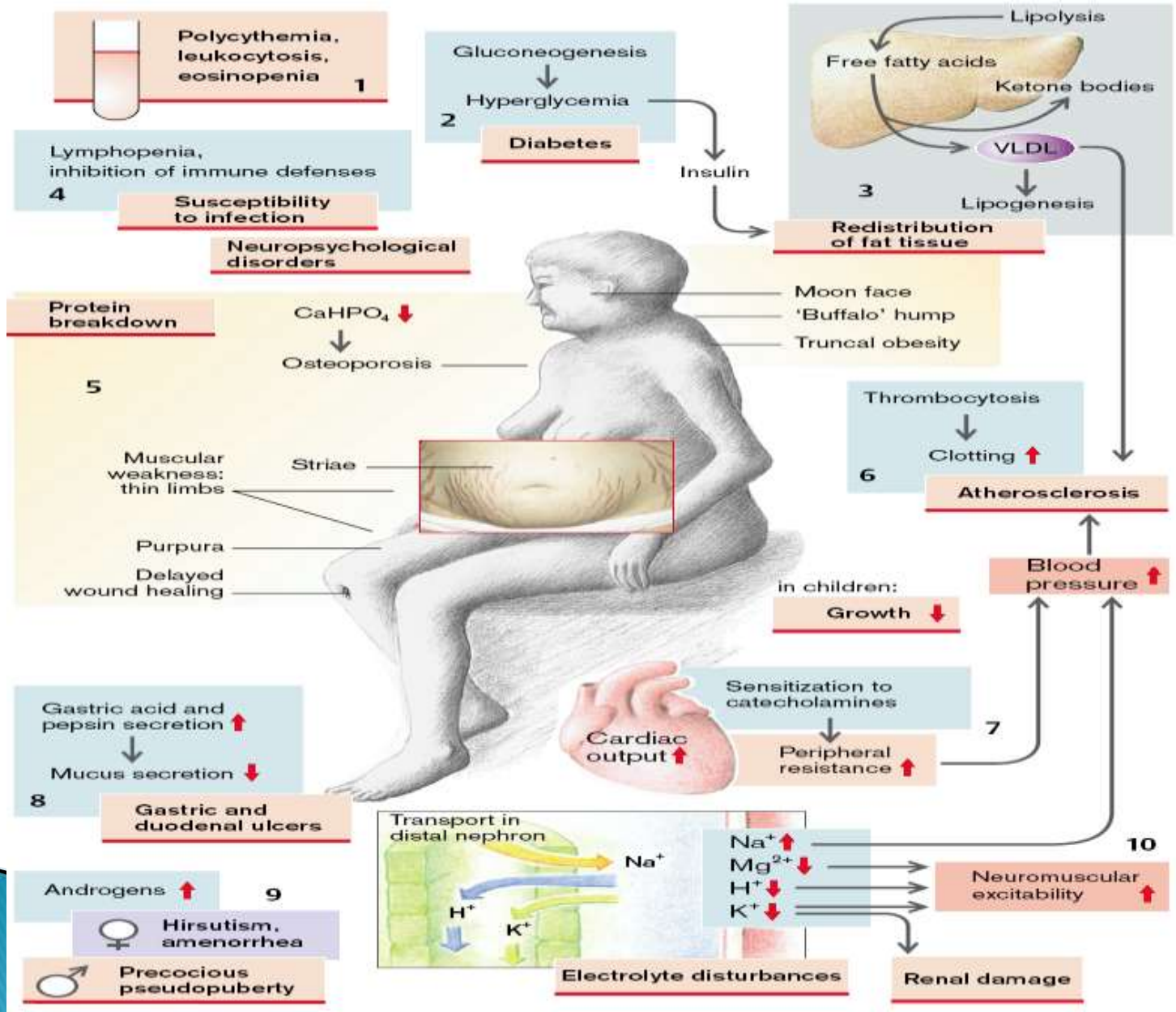
Efek Samping

- makin tinggi potensi, makin besar kemungkinan terjadi efek samping
- Efek lokal: penipisan kulit (dpt membaik saat tx dihentikan), perburukan kondisi infeksi, dermatitis kontak, jerawat pada tempat pemberian, hipopigmentasi reversibel, teleangiektasis menetap, dan striae atrophica
- Efek sistemik: penyerapan melalui kulit dapat menyebabkan supresi sumbu pituitari – adrenal, gangguan pertumbuhan dan Sindroma Cushing

Perhatian Khusus

- Preparat dengan potensi rendah merupakan pilihan untuk daerah wajah dan perlipatan.
- Preparat dengan potensi sangat tinggi sebaiknya tidak digunakan untuk anak di bawah 1 tahun.
- Preparat potensi sedang dan tinggi jarang menimbulkan masalah jika digunakan kurang dari 3 bulan.
- Preparat dengan potensi rendah jarang menimbulkan efek samping.

Efek Samping Pemakaian Glukokortikoid jangka panjang



Efek Samping

- Adrenocortical insufficiency: Suppression of HPA
- Adrenocortical excess (Cushing's disease): "Moon face", "buffalo hump"
- Diabetes Mellitus
- CNS effects: psychological and behavioral changes; aggravation of pre-existing psychiatric disorders.
- Impaired wound healing
- Musculoskeletal effects: osteoporosis (brittle bones), muscle weakness and atrophy
- Cardiovascular effects: fluid retention, edema, hypertension.

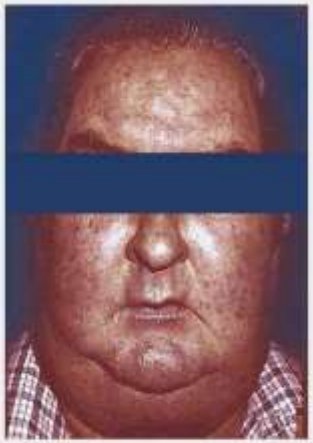
Glucocorticoid Withdrawal: Should be performed slowly

Withdrawal syndrome: hypotension, hypoglycemia, myalgia and fatigue

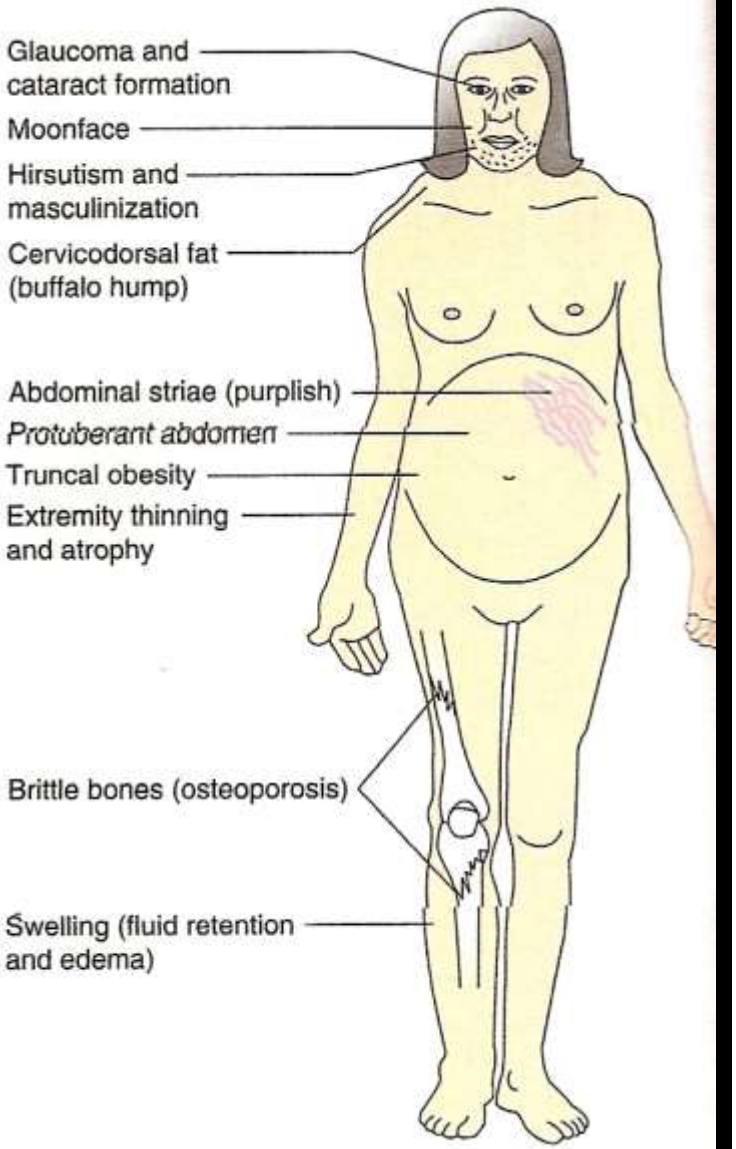
Cushing Syndrome (Hypercorticism)

Some cardinal signs of Cushing syndrome include:
Moon face
Glaucoma and cataract formation
Hirsutism and masculinization
Cervicodorsal fat (buffalo hump)
Extremity thinning and atrophy
Abdominal striae (purplish)
Protuberant abdomen
Truncal obesity
Swelling (fluid retention and edema)
Brittle bones (osteoporosis)

"Buffalo Hump"



"Moon Face"



Strategi Mencegah ES Jangka Panjang Kortikosteroid

- Pemberian dengan dosis intermitten (alternate-day), mis. setiap 2hari sekali
- Pemberian yg berefek lokal : topikal atau inhalasi

Drug Interactions

- Drugs that Enhance Corticosteroid Effects
  - Estrogens
  - Oral contraceptives
  - Antifungal agents
  - Antibiotics
  - *all of these agents inhibit cytochrome P450 enyzymes

- Drugs that Reduce Corticosteroid Effects
  - Antacids
  - Cholestyramine
    - *these drugs decrease the absorption of corticosteroids
  - Phenytoin: activate cytochrome P450 enyzymes

DRUG ALLERGY

KLASIFIKASI ESO

- Efek farmakologik berlebihan (mis. Hipotensi ok Anti HT)
- Gejala putus obat
- ES yang tdk berupa efek farmakologik utama (mulut kering ok efek antikolinergik TCA)
- ES akibat penggunaan jangka panjang (toleransi, ES lain)

DAPAT DIPREDIKSI

- Reaksi alergi
- Reaksi ok faktor genetik
- Reaksi idiosinkrasi

TIDAK DAPAT DIPREDIKSI

Reaksi allergi

- Allergi obat = efek obat pada pasien yg sebelumnya sdh pernah terpapar, tersensitisasi dan membentuk antibodi thd obat tsb.
- Mekanisme immunologik yg melatarbelakangi bervariasi dan kompleks.

Immunologically mediated reaction

Tipe	Reaksi	Jenis reaksi	Obat
I	IgE-dependent reactions	Urtikaria, angioedema, anafilaksis, hay fever	NSAID, penisilin,
II	Cytotoxic reactions, Ig G	Hemolisis, purpura	Penisilin, sefalosporin, sulfonamid, rifampisin
III	Immune complex reactions	Vasculitis, serum sickness	Quinidin, salisilat, chlorpromazine, sulfonamid
IV	Delayed-type reaction/ Cell mediated hypersensitivity	Dermatitis contact, reaksi exanthematous, reaksi photoallergic	Mekanisme tersering Banyak obat (topikal & sistemik)

SYOK ANAFILAKTIK

Clinical Features of Anaphylaxis

- Is there a predisposition? Latex and food allergies usually occur against a background of atopy and other allergic disorders e.g. asthma and eczema.

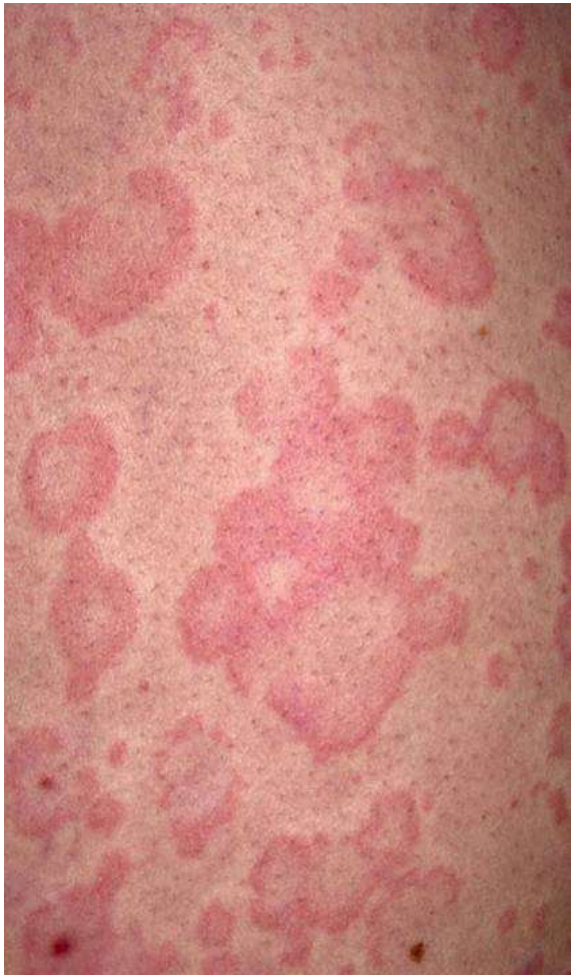
- Onset is rapid (5-10 minutes of exposure) peaking in 30 minutes. Duration can be long especially if allergen persists (e.g. swallowed) or the response is biphasic (classical 'late-phase' allergic response in the airways)

- May be heralded by impending sense of doom. Subsequent features reflect to some extent route of allergen exposure:

• **Systemic** (IV drugs) - cardiovascular (hypotension/syncope)
• **Ingested** (food allergens) - respiratory (laryngeal oedema/bronchoconstriction)
• **Percutaneous** (insect stings) - respiratory or cardiovascular problems equally likely

All may be accompanied by cutaneous features
e.g. urticarial rash.

Urticarial Rash

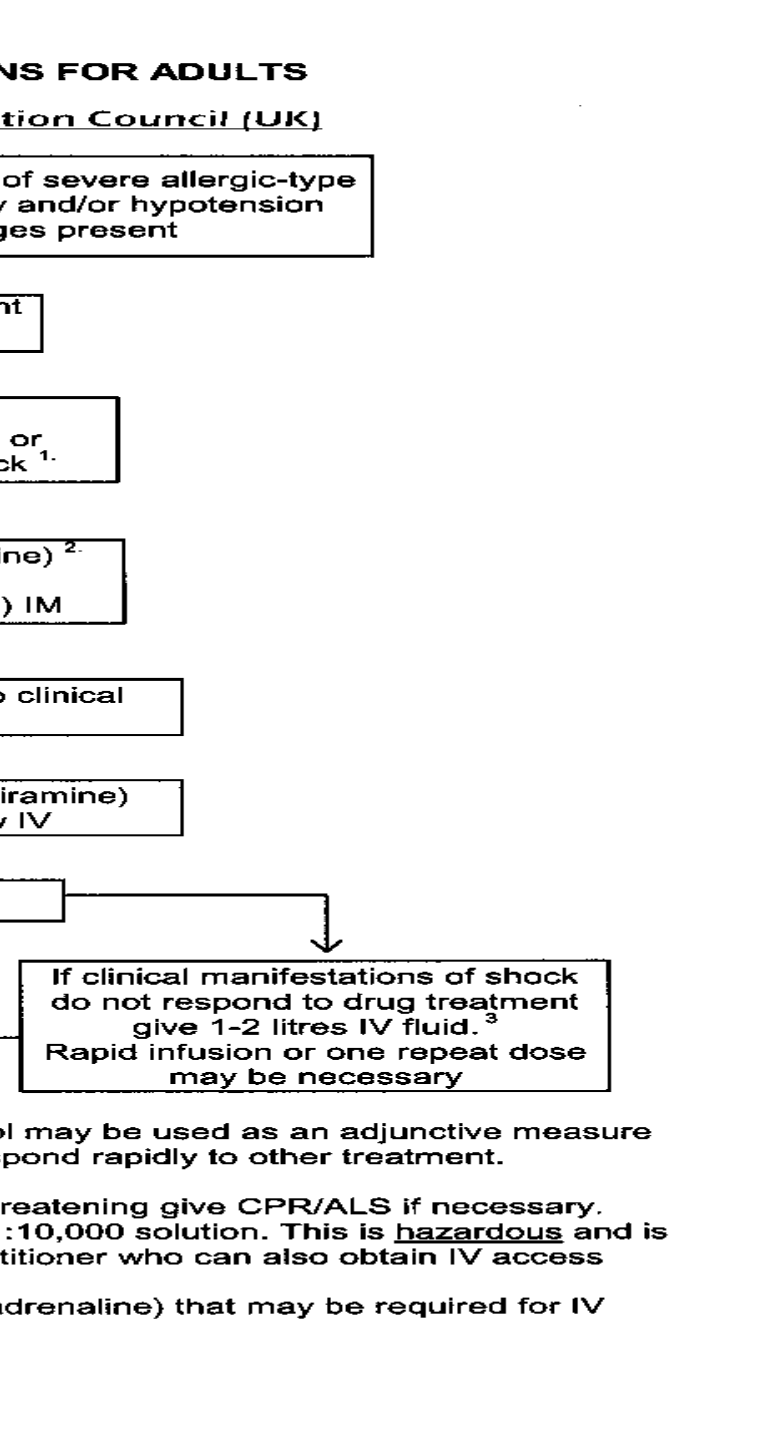


Features Suggesting Severe Anaphylactic Reaction

- **Wheeze**
- **Stridor**
- **Cyanosis**
- **Skin Pallor***
- **Prominent Tachycardia****

* 80% of fatal food-related anaphylactic reactions have no skin signs
** Compared to bradycardia in vasovagal attack

2005 Guidelines of the UK Resuscitation Council



NS FOR ADULTS

tion Council (UK)

of severe allergic-type
and/or hypotension
ges present

nt

or
ck [1].

ine) [2].
) IM

clinical

iramine)
IV

If clinical manifestations of shock
do not respond to drug treatment
give 1-2 litres IV fluid. [3]
Rapid infusion or one repeat dose
may be necessary

l may be used as an adjunctive measure
pond rapidly to other treatment.

reatening give CPR/ALS if necessary.
:10,000 solution. This is hazardous and is
titioner who can also obtain IV access

drenaline) that may be required for IV

EPINEFRIN /ADRENALIN

- Bukan anti allergi, tp sering dipakai pd kasus allergi ➔1st line drug syok anafilaktik
- Mek kerja : agonis kuat resept α & β adrenergik
- Berfungsi :
  - ✓memberi efek antagonis thd efek mediator inflamasi pada otot polos
  - ✓Menghambat Ag-induced release mediator inflamasi dari sel mast

Terima kasih atas perhatiannya...