Skin Pharmacology

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Dermatologic Pharmacology

Variables affecting Pharmacologic Response:

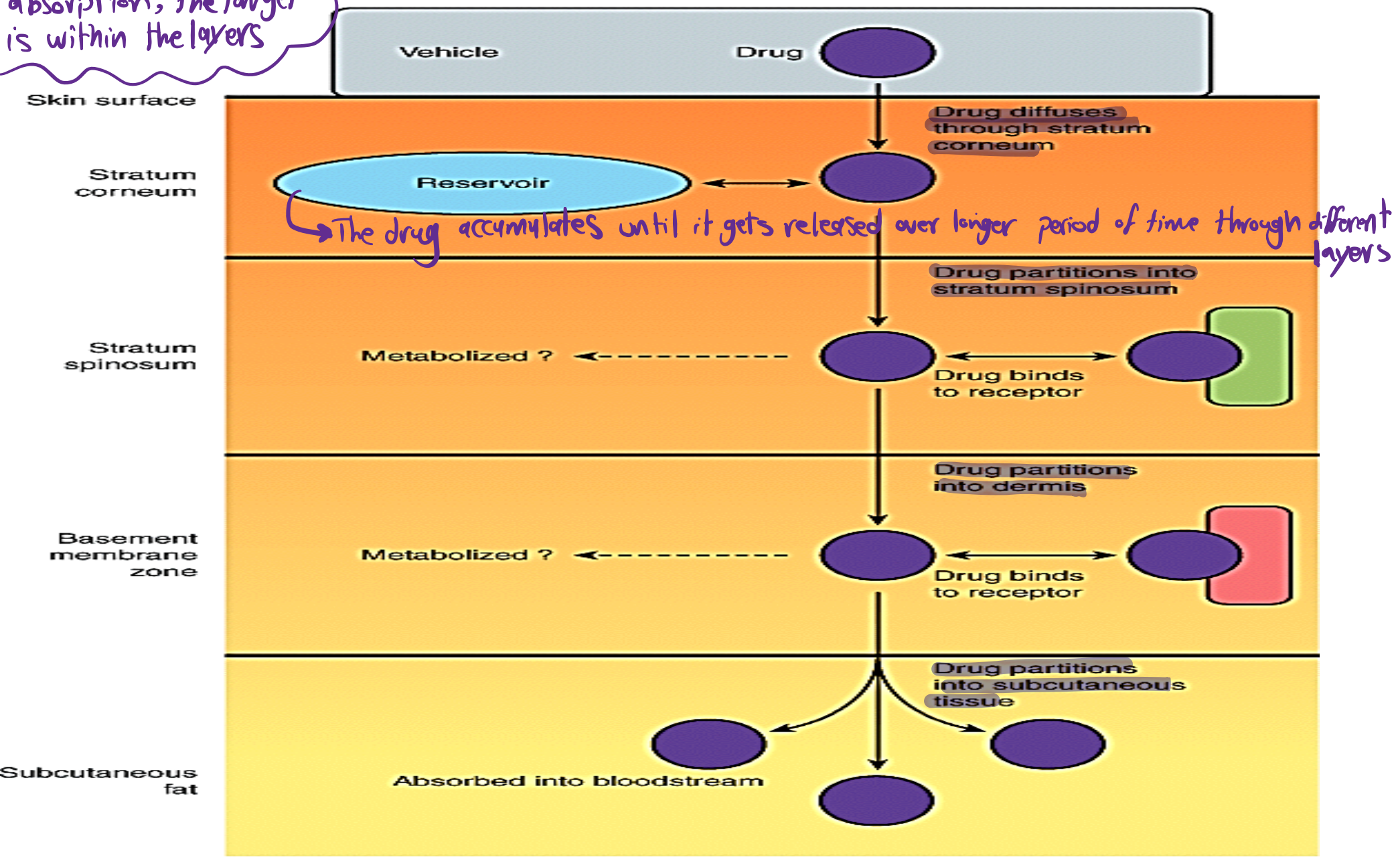
- **Regional variation in drug penetration.**
  - → mediate the penetration of the drug
- **Concentration gradient.** topical drugs moves from high conc. outer layer of the skin into the lower conc. inner layers
- **Dosing schedule.**
- **Vehicles and occlusion.** → The material that we put the drug in to transfer the drug to our body
  - Help us in determining which drug formulation to use depending on the area of the skin it's applied to (cream-gel-serum shampoo ....)
  - occlusion: Something to cover the skin with (tape, gloves...)
  - Helps to maintain the concetration gradient longer time

→ we can't apply the same formulation of a drug without taking into consideration those structural differences. (ex) The skin of the outer part of the hand is more keratinized compared with its inner part (more keratinized = more resistant to the permeation of the drug)

(ex) The area surrounding the eye is very thin and sensitive.

Here our drug works locally, no systemic absorption, the target is within the layers

Percutaneous Absorption.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: http://www.accessmedicine.com
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Differences between topical drug formulations

More water content ←

→ More lipophilic Vaseline-like content

Water - Lotion - Cream - Ointment - Vaseline

↳ more water content

↳ more lipophillic content

(ex) A very hyperKeratinized area is more resistant, so we need vaseline like structure so the drug can penetrate (Moisturize)

* Notice the difference between penetration/permeation and Absorption →

penetration of the drug across skin layers to reach inner part of the skin ←

movement of the drug into the circulation (usually we don't want a topical drug to reach circulation and cause systemic adverse effects)

Dermatologic Formulations

- **Tinctures.** → Alcohol based drug (Iodine)
- **Wet dressings.**
- **Lotions.**
- **Gels.**
- **Powders.** (help drying infected area as an anti bacterial powder)
- **Pastes.**
- **Creams.**
- **Ointments.**

Adverse Effects of Dermatologic Preparations

- Burning or stinging sensation.
- Drying and irritation
- Pruritus.(itch)
- Erythema.
- Sensitization.
- Staining
- Superficial erosion.

⇒ Advantages of topically administered drugs

- quick delivery to the site of action

- limiting systemic circulation reach eventually limiting systemic adverse effects

TABLE 61–1

Local cutaneous reactions to topical medications.

*Don't worry about this table, it's more related to immunology, so don't get into its details

Reaction type	Mechanism	Comment
Irritation	Non-allergic	Most common local reaction (caused by alcohol based drugs most of the time)
Photoirritation	Non-allergic	Phototoxicity; usually requires UVA exposure (such drugs can't be objected light)
Allergic contact dermatitis	Allergic	Type IV delayed hypersensitivity
Photoallergic contact dermatitis	Allergic	Type IV delayed hypersensitivity; usually requires UVA exposure
Immunologic contact urticaria (شرية)	Allergic	IgE-mediated type I immediate hypersensitivity; may result in anaphylaxis
Non-immunologic contact urticaria	Non-allergic	Most common contact urticaria; occurs without prior sensitization

F

Compared with the immunologic type that don't produce a reaction upon the first exposure, not until the formation of IgE.

Topical Antibacterial Agents

- **Gram-positive bacteria**
  - **Bacitracin**
  - **Gramicidin**
  - **Fusidic acid**

Antibiotic x Antibacterial
- it's produced from a natural source (penicillin) and it can be antibacterial antifungal, antiviral....
- chemically synthesized

- **Gram-negative bacteria**
  - **Polymyxin B Sulfate**
  - **Neomycin**
  - **Genatamicin**

* highlighted things are what doctor stressed on
* Don't memorize any spectrum of action (names of organisms targeted)

BACITRACIN

spectrum of action isn't required ^^

- Active against streptococci, pneumococci, and staphylococci
- Also , most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive.
- MOA??? Mechanism of Action: cell wall synthesis inhibitor

Related to topical administration

- Side effects: Toxicity ???

  Allergic contact dermatitis occurs frequently, and immunologic allergic contact urticaria rarely. Bacitracin is poorly absorbed through the skin, so systemic toxicity is rare.

Advantage

* can cause renal toxicity, that's why it's not administered systemically

- Regarding absorption of drugs, a patient with large areas of burn can't be given a drug with serious systemic toxicity, because he has higher chance of absorbing this drug with his denuded skin.

Since skin infections are usually caused by more than one organism at a once

- Frequently used in combination with other agents (polymyxin B and neomycin)
- Form: creams, ointments, and aerosol preparations
- Usually Antiinflammatory agents added
  - (Hydrocortisone) ⇒ to reduce systemic side effects as well as inflammatory reactions (swelling, itching, redness....) (it can be alone for those inflammatory responses)

Fusidic acid

- **acts as a bacterial protein synthesis inhibitor**
- **Staphylococcus species, Streptococcus species, and Corynebacterium species.**

- often used topically in creams and eyedrops

POLYMYXIN B SULFATE

- gram-negative :Pseudomonas aeruginosa, Escherichia coli, enterobacter, and klebsiella.
- Proteus and serratia are resistant, as are all gram-positive organisms.
- Side effects: total daily dose applied to denuded skin or open wounds should not exceed 200 mg in order to reduce the likelihood of toxicity "neurotoxicity and nephrotoxicity"
  - Allergic contact dermatitis NOT common.

like burned skin

only if systemic absorption occurs

NEOMYCIN & GENTAMICIN

Neomycin

- Aminoglycoside antibiotics → protein synthesis inhibitors / bacteriostatic
- gram-negative :E coli, proteus, klebsiella, and enterobacter.
- SE: allergic contact dermatitis

- Gentamicin generally shows greater activity against P aeruginosa than neomycin.
- Gentamicin more active against staphylococci and group A β-hemolytic streptococci.
- Be careful with systemic toxicity : esp in renal failure → low Renal Clearance → Renal or nephrotoxicity (only if absorbed systemically)
- Hospital acquired resistant

Acne treatment

- **One of the most common skin diseases presenting to family physicians**
- **Considerable psychological impact on the quality of life**
- **Four main factors cause acne:**
  - **Excess oil (sebum) production.** (or accumulation of sebum in clogged pores)
  - **Hair follicles clogged by oil and dead skin cells.**
  - **Bacteria.** (mainly caused by bacteria)
  - **Inflammation** (Acne can be a body's way to respond to an inflammation)
  - Hormonal disturbances (depending on the cyclical variation of the hormonal level)
- **The anaerobic bacterium Cutibacterium acnes (Propionibacterium acnes) is believed to play an important role in the pathophysiology of the common skin disease acne vulgaris.**

Spectrum of Acne lesions

Comedonal Lesions

due to excessive production of oil

Black heads

Inflammatory Lesions

More exaggerated inflammatory response (more red, more elevated, more pus)

Nodulocystic Lesions

More developed condition (bigger pumps with more pus and more widespread in the body)

* Here we would need systemic administration of antibacterial agents

Scaring

if left without treatment, scarring occurs and it's difficult to treat
(treated by filler or collagen injections, laser treatment)

Topical Therapy (Indications)

- Indications (when to use)

- **comedonal acne**
- **mild to moderate inflammatory acne**

Topical Therapy *(Treatment Vehicle)* (depending on skin type)

- **cream → sensitive or dry skin**
- **lotion → any skin type**
- **gel → oily skin**
- **solution → oily skin**

more watery ↓

Topical Therapy (Anti Comedonal Agents)

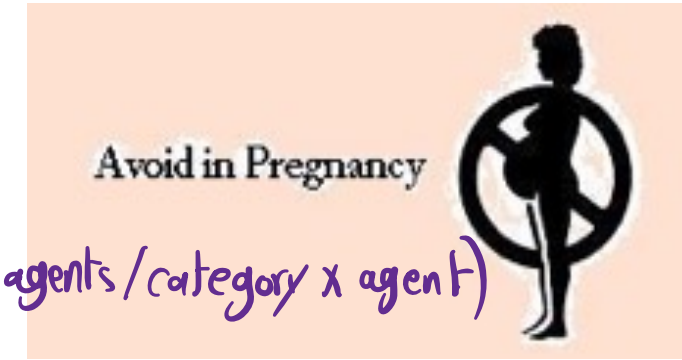
- **Topical Retinoids 0.025% - 0.5%**
- **Azelaic acid**
- **Salicylic acid**

Topical Retinoids (Adapalene (Differin))

Scientific name

commercial name

- **Topical Retinoids 0.025% - 0.5%** (vitamin A derivatives)
  - **apply at night**
  - **always apply test dose** (to make sure it won't cause an allergic reaction)
  - **start at low concentrations**
  - **avoid in pregnancy** (it's a teratogenic agents / category X agent)



- **Side Effects:**
  - **pustular flare** (pus containing pimples) "initially"
  - **photosensitivity** better used indoor, and use sunblock
  - **skin irritation and erythema**
  - **dryness and peeling**

Azelaic Acid 20%

- **competitive inhibitor of mitochondrial oxidoreductases and of 5 alpha-reductase, inhibiting the conversion of testosterone to 5-dehydrotestosterone. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including Propionibacterium acnes**

→ responsible for secondary sex characteristics, a hormone that is involved in the formation of acne

- **applied twice daily**
- **Side Effects**

- **erythema and irritation**
- **decrease in pigmentation**

Salicylic Acid 0.5 - 2%

- **keratolytic. It belongs to the same class of drugs as aspirin (salicylates)**
- **Can reduce swelling and redness and unplugging blocked skin pores to allow pimples to shrink**
- **applied twice daily**
- **skin dryness and irritation**

Topical Therapy (Anti Inflammatory Agents)

- **Benzoyl Peroxide 2.5 - 10%**

exhibits bactericidal effects against Cutibacterium acnes (usually in the form of solution)

- **apply once to twice daily**
- **always apply test dose**
- **avoid use at night**
- **dryness of skin**

+ it's also used in combination

- it's very irritant, not for long time or overnight use
- it cause bleaching of cloths

Topical Therapy (Anti Inflammatory Agents)

- Clindamycin.
- Erythromycin.

protein synthesis inhibitors (50s of ribosomes)

  - apply twice daily
  - skin dryness

Combination therapy

- 5% Benzoyl Peroxide and 3% Erythromycin
- 5% Benzoyl Peroxide and 1% Clindamycin
- Topical antibiotics and Azelaic acid or Tretinion

like adapalene

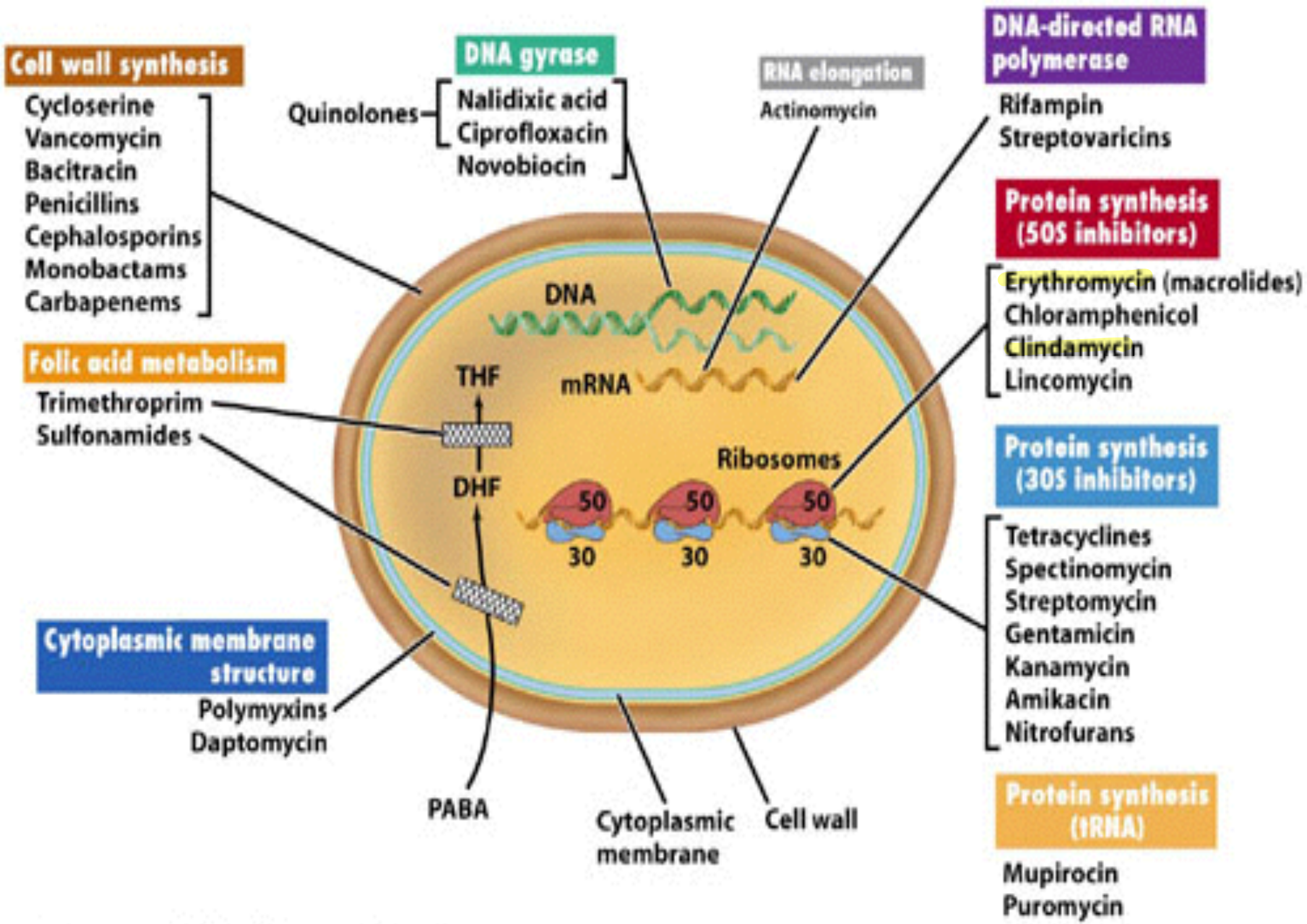


Figure 20-14 Brock Biology of Microorganisms 11/e

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Clindamycin

- **10% absorbed, so, possibility of *Pseudomembranous colitis***
- The hydroalcoholic vehicle and foam formulation (Evoclin) .....may cause drying and irritation of the skin, with complaints of burning and stinging.
- The water-based gel and lotion formulations..... well tolerated and less likely to cause irritation. *Allergic contact dermatitis is uncommon.*
- Clindamycin is also available in fixed-combination topical gels with benzoyl peroxide (Acanya, BenzaClin, Duac), and with tretinoin (Ziana).

treated by metronidazole/vancomycin

systemic side effect

since it's alcohol based

Don't memorize commercial names

Erythromycin

- In topical preparations, erythromycin base rather than a salt is used to facilitate penetration ⇒ not important
- One of the possible complications of topical therapy is the development of antibiotic-resistant strains of organisms, including staphylococci
- Adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin
- Clindamycin is also available in fixed-combination topical gels with benzoyl peroxide (Acanya, BenzaClin, Duac), and with tretinoin (Ziana). Don't memorize commercial name

Metronidazole (against bacteria and parasites)

- Effective in the treatment of rosacea. الوردية
  Dilation of skin blood vessels

- Rosacea: common skin condition that causes blushing or flushing and visible blood vessels in your face. It may also produce small, pus-filled bumps. These signs and symptoms may flare up for weeks to months and then go away for a while

Metronidazole

- The mechanism of action is unknown
  - but it may relate to the inhibitory effects of metronidazole on Demodex brevis; This drug may act as an anti-inflammatory agent by direct effect on neutrophil cellular function
  - Adverse local effects include dryness, burning, and stinging.
  - Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

a parasite involved in the inflammatory responses of rosacea

Reducing

Systemic therapy

Indications:

- **Moderate inflammatory acne non-responsive to topical therapy**
- **nodulocystic acne**

Systemic therapy

- **Oral Antibiotics**
- **Isotretinoin**
- **Hormonal Therapy**

Oral Antibiotics (used for 3-6 months)

(usually those antibiotics are given for long period of time before we start to see results)

- **Tetracycline 500mg X BD**
- **Doxycycline 100mg X BD**
- **Minocycline 100mg X OD**
- **Eythromycin 500mg X BD**

BD : twice a day
OD : once a day

Don't memorize the doses

- **combined with topical therapy**

-if the patient can't tolerate side effects of antibiotics OR have been using them with no improvement, we can use isotretinoin

Isotretinoin (Accutane) indicated in

- **severe nodulocystic acne**
- **non responsive acne**
- **severe psychological distress**

Isotretnoin (RoAccutane) side effects

- **!teratogenic!** (Avoid during pregnancy and at least one month before getting pregnant)
- **mucosal dryness** (prescribed with moisturizer, eye drops)
- **photosensitivity**
- **arthralgias** (pain in muscles and joints)
- **alteration of liver enzymes** (ALT and AST tests are needed)
- **hypertriglyceridemia and hypercholesterolemia** (lipid profile checks are needed also)
- **Tumerogenic in animals** (can cause certain types of cancer)

patient should be very careful not to get pregnant

* it can also cause psychological effects (depression)

Isotretnoin (RoAccutane)

Why it's considered a desquamative agent ?

- Retinoic Acid(Tretinoin): is the acid form of Vitamin A. Stabilizes lysosomes, increases RNA polymerase activity, increases PGE_2, cAMP, and cGMP levels, and increases the incorporation of thymidine into DNA. On molecular level

- Decreases cohesion between epidermal cells and increases epidermal cell turnover. This will result in expulsion of open comedones and the transformation of closed comedones into open ones. phsiologically

  → No Cohesion – cells start shedding – this opens up comedones – everything gets cleared out

- Also, promotes dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles. "Baby SKin"

This medication is taken from 6–9 months, the dose depend on the patient weight.

Drugs for Psoriasis الصدفية

- **Acitretin:** (Vitamin A derivative)
  - Related to isotretinoin.
  - Given orally.
  - Hepatotoxic and teratogenic. (More toxic than isotretinoin)
  - Patients should not become pregnant for 3 years after stopping treatment, and also should not donate blood.

Drugs for Psoriasis

(The first choice for treatment of psoriasis is cortisone cream, and if it's not responding we use ↙

- **Tazarotene:** (vitamin A derivative)
  - Topical. (can be used to treat acne)
  - Anti-inflammatory and antiproliferative (→ for bacteria) actions.
  - Teratogenic. Also, can cause burning, stinging, peeling, erythema, and localized edema of skin.

Side effects related to topical application

- **Calcipotiene:**
  - Synthetic vitamin D_3 derivative

MOA is not known

New Drugs for Psoriasis

Apremilast(Otezla)

- psoriasis and psoriatic arthritis.
- It may also be useful for other immune system-related inflammatory diseases.
- The drug acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) and inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells.

Side Effects

- diarrhea
- nausea.
- stomach pain.
- vomiting.
- headache.
- sore throat, cough, and fever.
- sneezing, runny nose, and nasal congestion.e-to-severe psoriasis demonstrating superior efficacy to apremilast

New Drugs for Psoriasis

Deucravacitinib (Sotyktu)

- A new oral treatment option for adults with plaque psoriasis.
- moderate-to-severe plaque psoriasis
- It is a once-daily oral medication with its clinical trials in moderate-to-severe psoriasis demonstrating superior efficacy to apremilast
- MOA: Allosteric inhibitor of TYK2
- Side effects:runny nose, congestion, or sore throat, sore on mouth, lips, gums, tongue or roof of mouth, acne.

New Drugs for Psoriasis

Topical drugs

Roflumilast (Zorvye) cream

selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4). It has anti-inflammatory effects

- chronic plaque psoriasis
- an effective topical therapy for use on all psoriasis-affected areas including body, face, and intertriginous areas

folds of our body

Tapinarof (Vtama) is a topical (on the skin) medication used to treat plaque psoriasis in adults.

- MOA: immune modulation, skin-barrier normalization, and antioxidant activity.

suppresses immune cells

- It's convenient to use because it's only applied once daily

Drugs for Psoriasis

- **Biologic Agents:** Antibodies
  - **Alefacept:**
    - Immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG_1.
  - **Efalizumab:**
    - Recombinant humanized IgG_1 monoclonal antibody.
    - Withdrawn (because it causes) :progressive multifocal leukoencephalopathy (PML),
    - Can cause thrombocytopenia.
  - **Etanercept:** given IV
    - Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG_1.

Anti-inflammatory Agents

- **Topical Corticosteroids:** ⇒Main therapy of psoriasis
  - (ex) Hydrocortisone.
  - Prednisolone and Methylprednisolone.
  - Dexamethasone and Betamethasone.
  - Triamcinolone. (intralesional injection for the treatment of scars)
  - Fluocinonide.

- They mainly inhibit the production of Arachidonic acid (a central inflammatory mediator) through inhibition of phospholipase A2

Anti-inflammatory Agents

- **Topical Corticosteroids:** Don't memorize them
  - **Absorption:** Different conc. depending on the area we're applying on
    - 1% of hydrocortisone applied to the ventral forearm.
    - 0.14 times of hydrocortisone applied to the plantar foot.
    - 0.83 times of hydrocortisone applied to the palm.
    - 3.5 times of hydrocortisone applied to the scalp.
    - 6 times of hydrocortisone applied to the forehead.
    - 9 times of hydrocortisone applied to the vulvar skin.

Anti-inflammatory Agents

- **Topical Corticosteroids:**
  - **Absorption:**
    - **Absorption increased with inflammation.**
    - **Increasing the concentration does not proportionally increase the absorption.**
    - **Can be given by intralesional injection.**

Triamcinolone for scars

Anti-inflammatory Agents

- **Topical Cortcosteroids:**
  - **Dermatologic disorders very responsive to steroids:**
    - **Atopic dermatitis.**
    - **Seborrheic dermatitis.**
    - **Lichen simplex chronicus.**
    - **Pruritus ani.**
    - **Allergic contact dermatitis.**
    - **Eczematous dermatitis.**
    - **Psoriasis**

Anti-inflammatory Agents

- **Topical Cortcosteroids:**
  - **Adverse Effects:**
    - Suppression of pituitary-adrenal axis.
    - Systemic effects.
    - Skin atrophy.
    - Erythema.
    - Pustules.
    - Acne.
    - Infections.
    - Hypopigmentation.
    - Allergic contact dermatitis.

most important side effect

Related to topical admin

↳ we have endogenous cortcosteroids produced by adrenal gland, it will stop being produced with higher exogenous circulating cortcosteroids, so if the patient stops the treatment suddenly he may go into crisis.

we worry about this effect with systemic administration

Agents affecting Pigmentation

There are certain conditions where we need to increase pigmentation of the skin in cases of depigmentation (albinism, vitiligo)

- **Trioxsalen.**
- **Methoxsalen.**

drugs that need to be activated by light

  - Are psoralens used for the repigmentation of depigmented macules of vitiligo. (بقعات)
  - Must be photoactivated by long-wave-length ultraviolet light (320-400nm) to produce a beneficial effect.
  - They intercalate with DNA.
  - Can cause cataract and skin cancer.

Agents affecting Pigmentation

Those drugs de-pigment the skin by preventing the biosynthesis of melanin

- **Hydroquinone.**
- **Monobenzone.**
- **Monobenzone may be toxic to melanocytes resulting in permanent depigmentation.**

it kills those cells

Here the patient have to avoid sunlight

- **Mequinol**
  - **Reduce hyperpigmentation of skin by inhibiting the enzyme tyrosinase which will interfere with biosynthesis of melanin.**

Trichogenic and Antitrichogenic Agents

increase hair growth

decrease hair growth

- **Minoxidil (Rogaine):** (Trichogenic)
  - Designed as an antihypertensive agent.
  - Effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia.
  - Vertex balding is more responsive than frontal balding.

used either topically or orally

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride (Propecia):** (Trichogenic)
  - **5á-reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterne.**
  - **Oral tablets.**
  - **Can cause decreased libido, ejaculation disorders, and erectile dysfunction.**

→ Side effects related to sexual functions

Trichogenic and Antitrichogenic Agents

- **Minoxidil.**
- **Finasteride.**
- **Eflornithine:** (Antitrichogenic)
  - **Is an irreversible inhibitor of ornithine decarboxylase, therefore, inhibits polyamine synthesis. Polyamines are important in cell division and hair growth.**
  - **Effective in reducing facial hair growth in 30% of women when used for 6 months.**