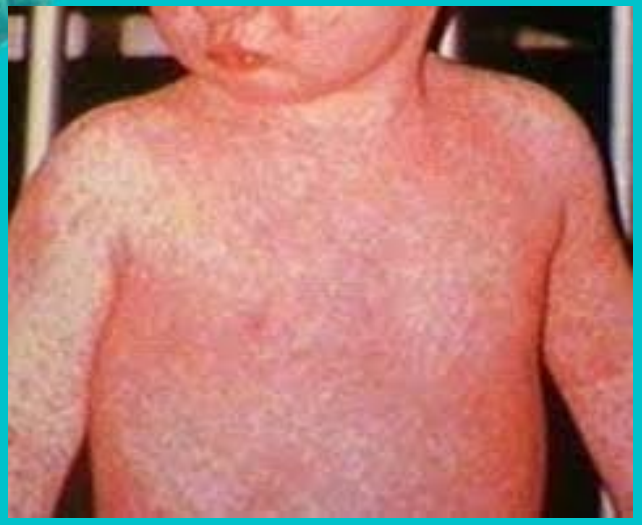
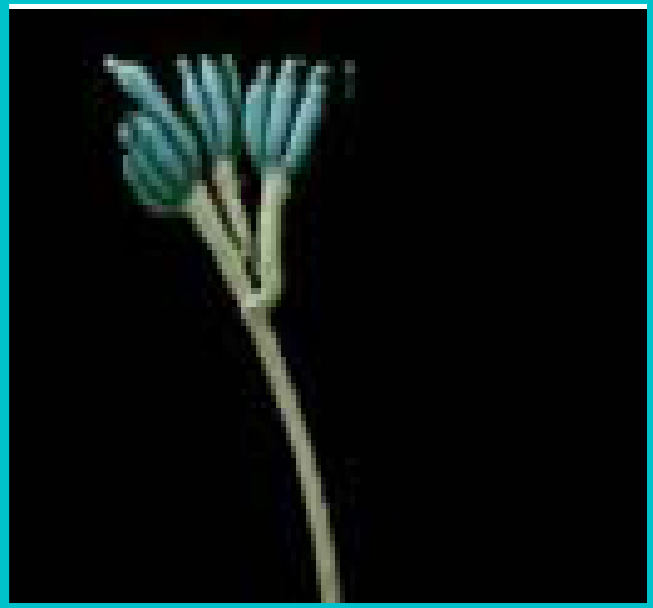
Clinical case

- An eight year boy who had sore throat with fever was given a penicillin as treatment. Within few hours of fist dose he develops severe rash



- What may be the reason for the rash?
- Was the prescription appropriate ?

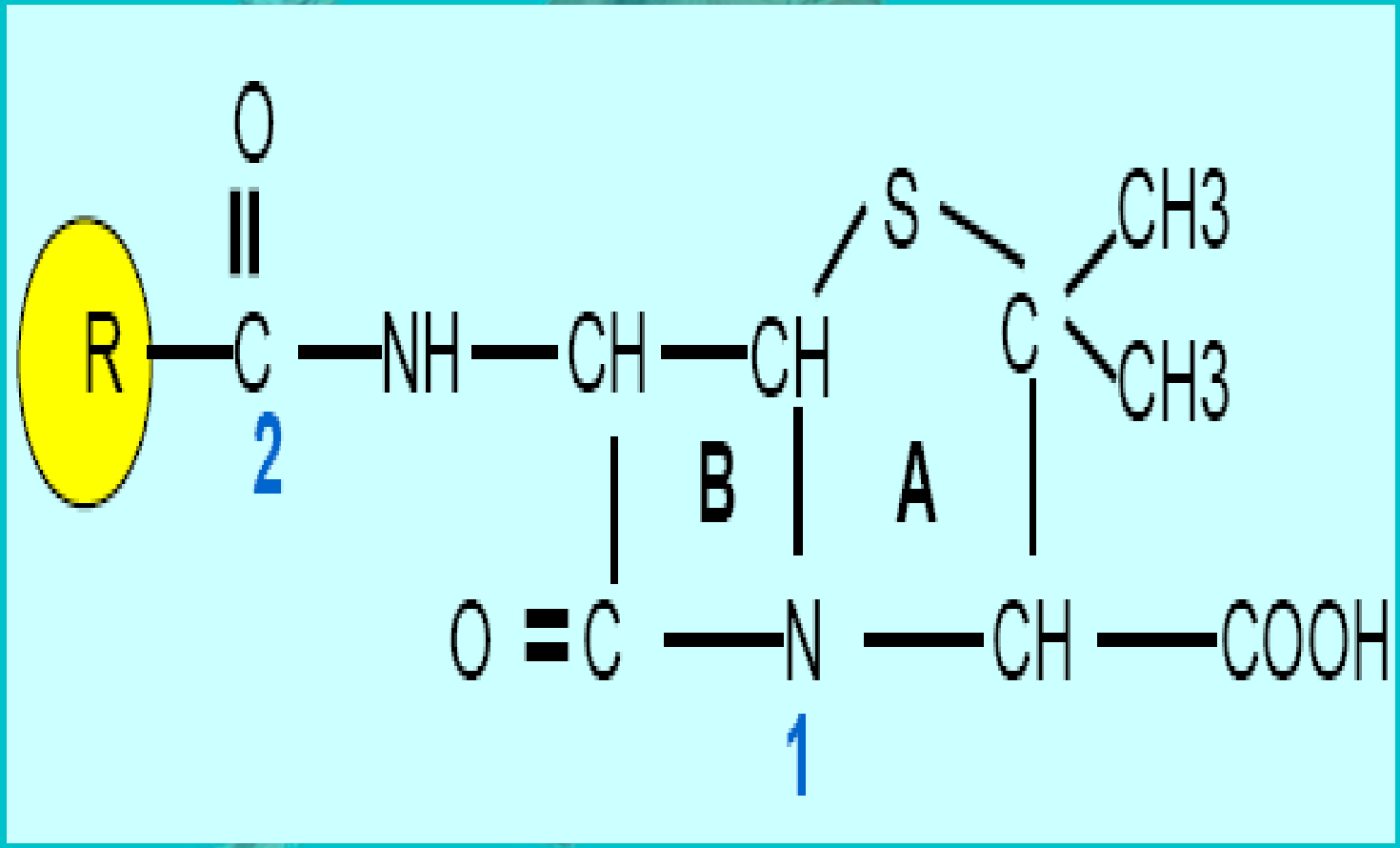
Penicillins

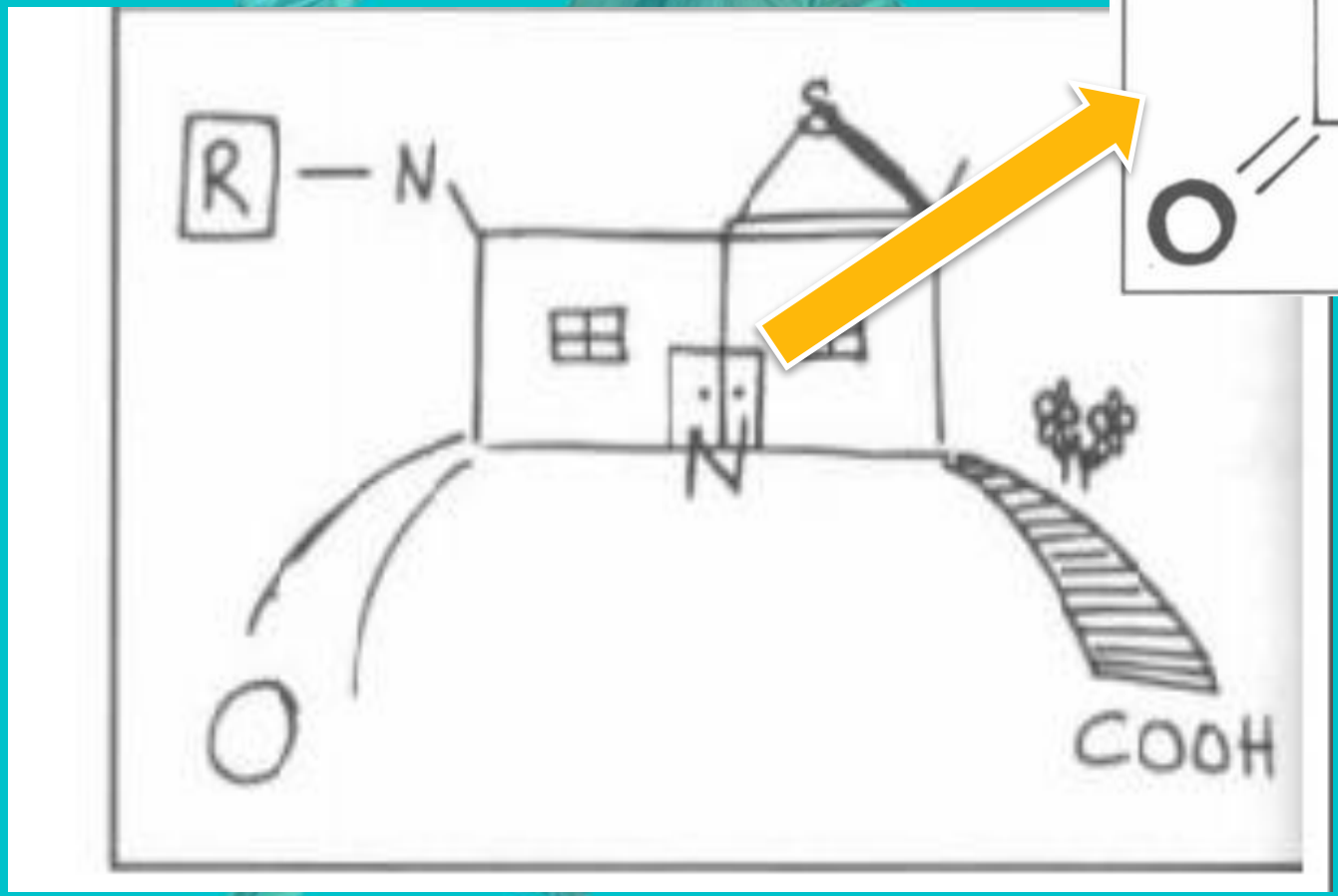


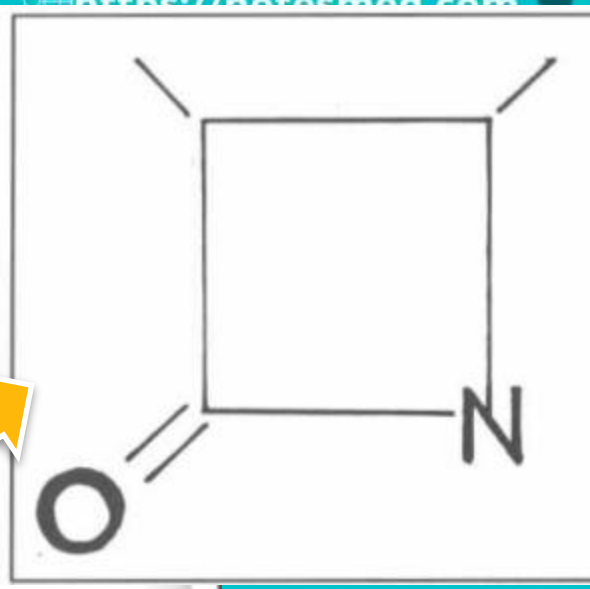
β-lactam Antibiotics

- Penicillins
- Cephalosporins
- Monobactam (Aztreonam)
- Carbapenems
- Penems

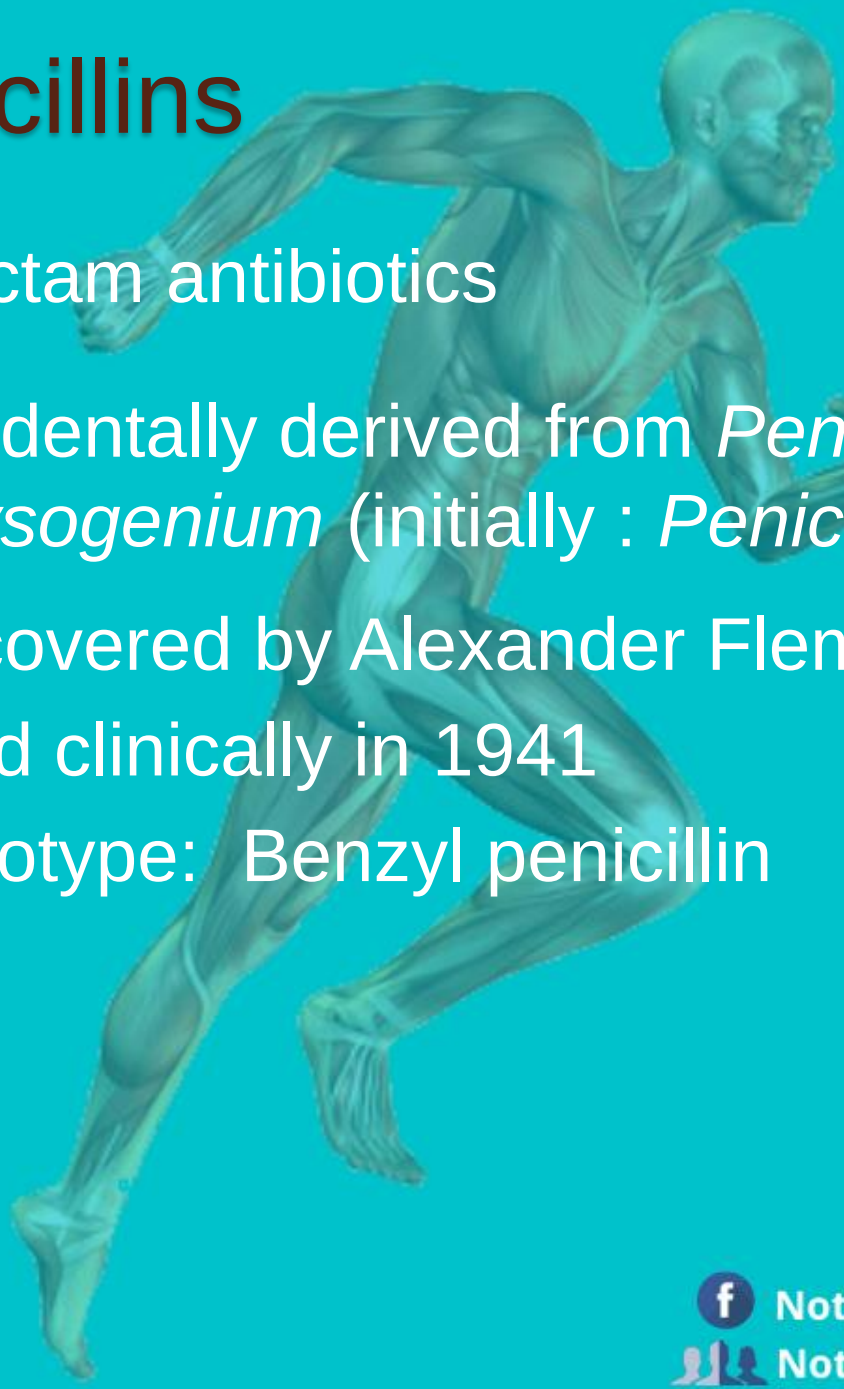
Structure of penicillins







Penicillins



- β-lactam antibiotics
- Accidentally derived from *Penicillium chrysogenium* (initially : *Penicillium notatum*)
- Discovered by Alexander Fleming (in 1929)
- Used clinically in 1941
- Prototype: Benzyl penicillin

Mechanism of action

- Cell wall synthesis inhibition by binding to penicillin binding proteins (PBPs) which include transpeptidase enzyme
- Inhibition of 'transpeptidase' by beta lactam ring

Prevent cross linking of NAM and NAG

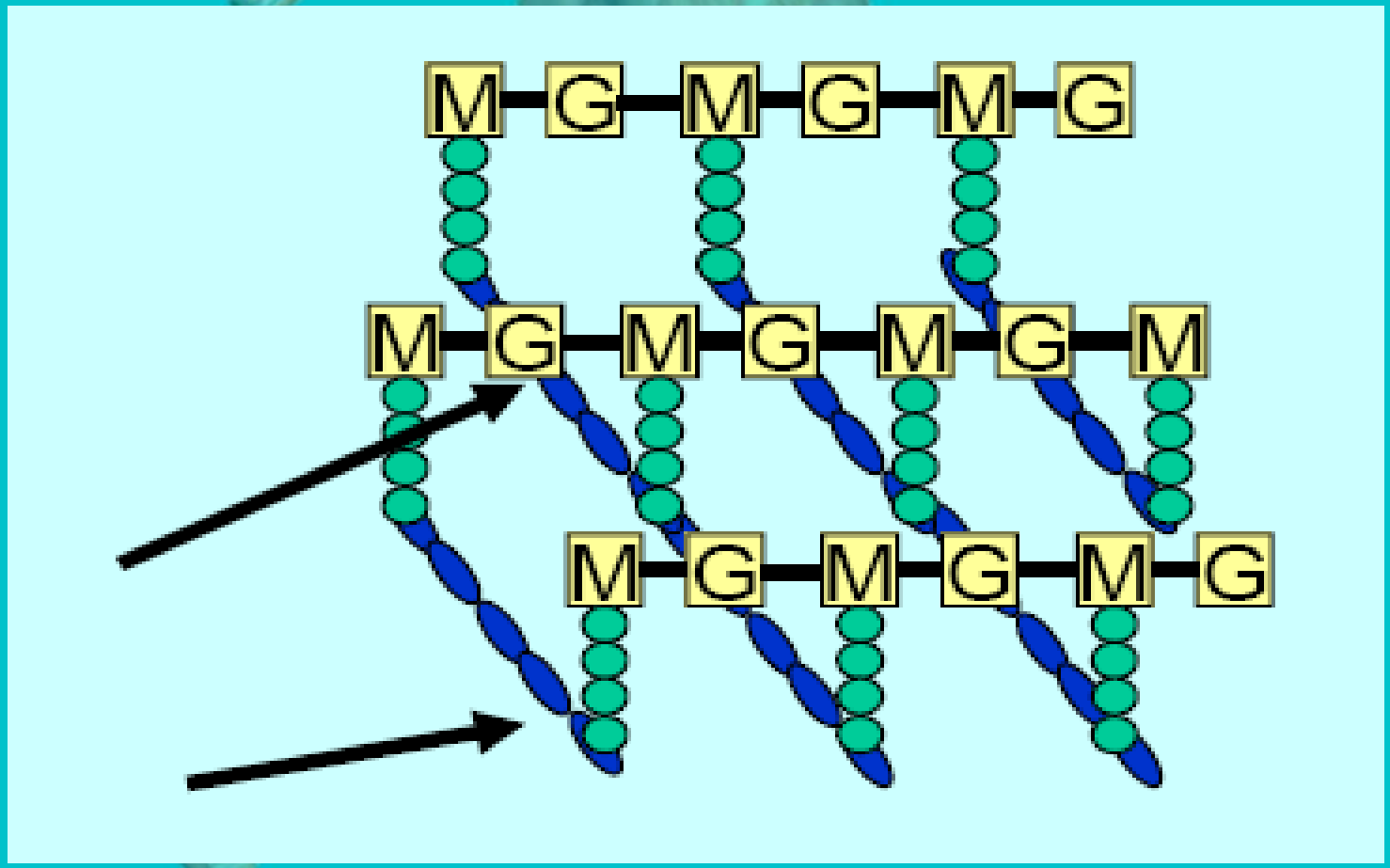
Lysis of cell (bactericidal)

NAM: N-acetyl-muramic acid
NAG: N-acetyl-glucosamine

Penicillins

- The penicillin must overcome the bacterial defenses and penetrate the outer cell-wall layers to the inner cytoplasmic membrane, where the PBPs including transpeptidase enzyme are located
- In gram-negative bugs, the penicillin must pass through channels known as porins
- Not interfered by blood, pus or tissue fluid
- Resistance may develop due to:
  - Penicillinase, mutation and tolerance

Cross Links in bacterial cell wall



- Penicillin V
- Aminopenicillins
- Isoxazolyl penicillins
- Carboxypenicillins
- Ureidopenicillins

Mechanism of bacterial resistance to penicllins

- By producing β-lactamases, which destroy the β-lactam ring for example S. aureus, E. coli, gonococci, H. influenzae, etc.
- Due to altered PBPs which have less affinity for β-lactams, for example: S. pneumoniae
- Due to decreased ability of drug to penetrate to its site of action.

Benzyl penicillin (Penicillin G)

- Primarily active against Gram +ve bacteria and very few gram –ve bacteria
  - Streptococci (except enterococci),
  - *Bacillus anthracis*, *Cl. diphtheriae Cl. tetani / welchi*
  - *Listeria*, *T. pallidum & Borrelia ,Leptospira*
  - Gonococci, meningococci
  - *E. coli* and proteus (some species)
- Acid-labile & also destroyed by

Pharmacokinetics

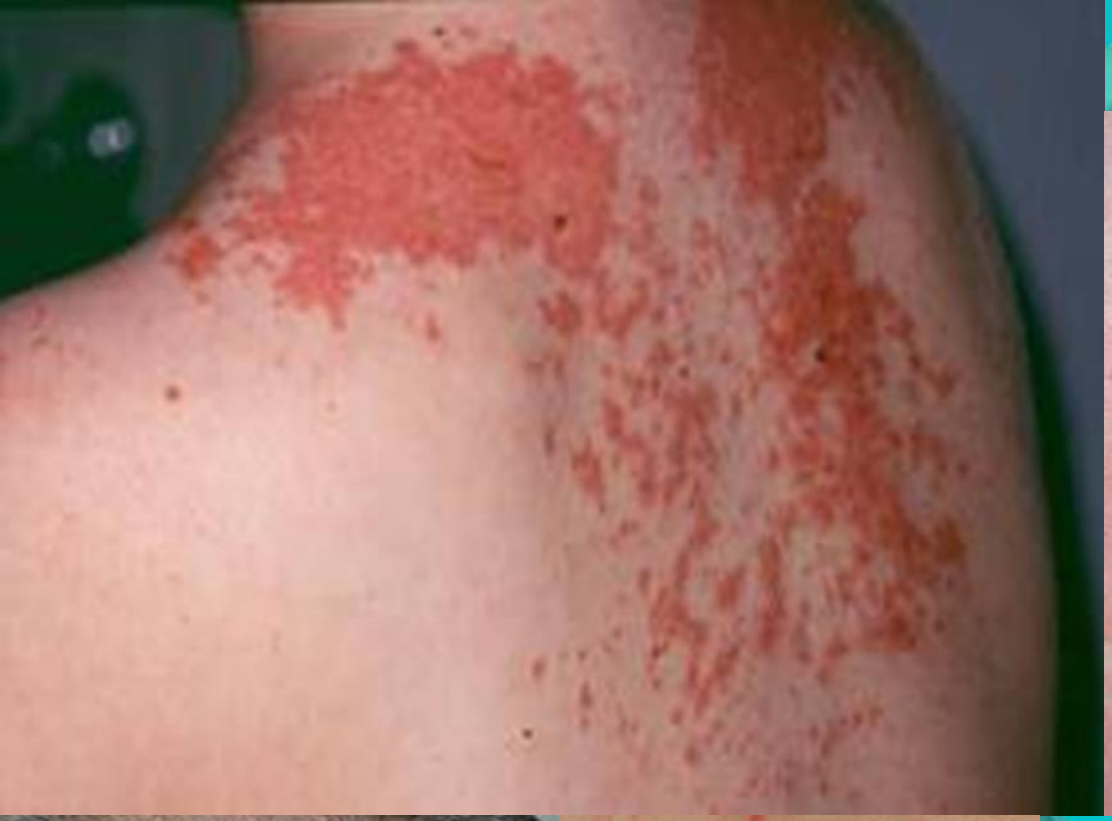
- Well absorbed when given IM, because when penicillin G given orally it is destroyed by gastric acid (acid labile)
- Distributed extracellularly (mainly)
  - Poor penetration through BBB or synovial membrane (except when inflamed)
- Excretion: Active Tubular secretion ~90%
  - Probenecid prevents it and prolongs its action

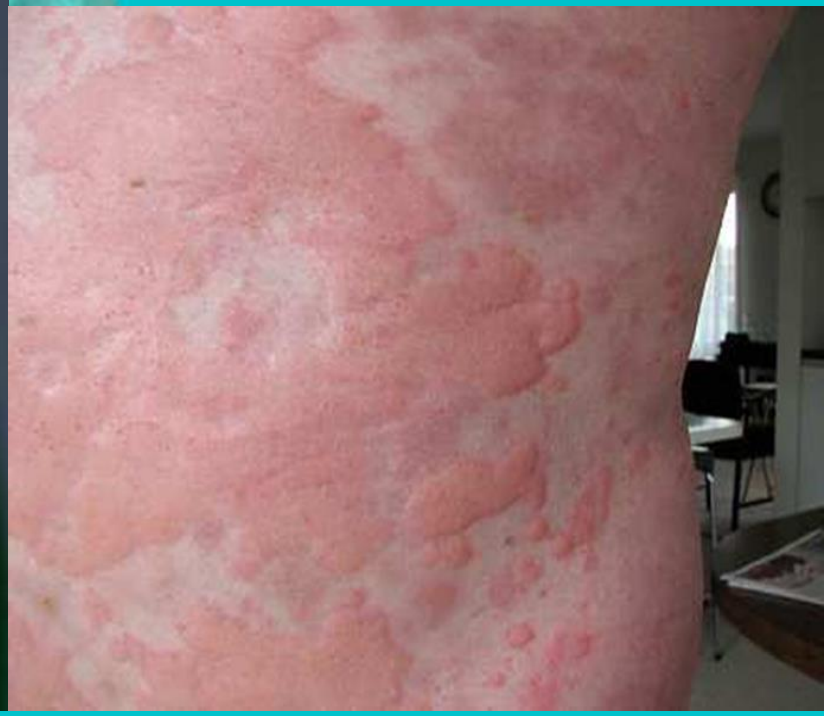
Penicillin G Preparations

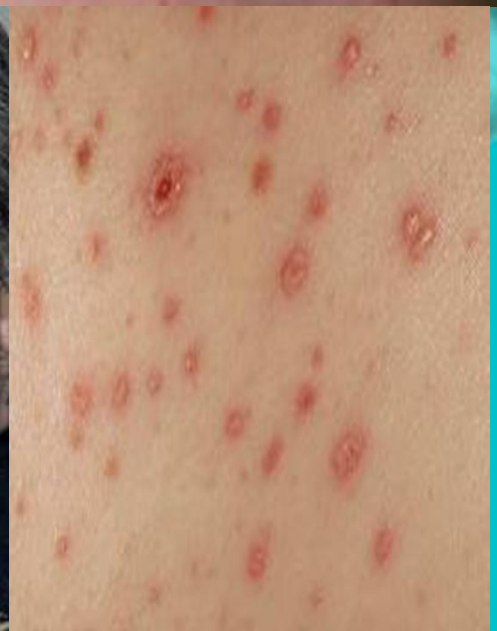
- Penicillin G (Na^+ or K^+ salts, Crystalline penicillin) : 6 hourly-- IV /IM
- Repository penicillins-- IM :
  - Procaine penicillin : 12 hourly
  - Benzathine penicillin : every 2 - 4 weeks
    - Should not be given IV : Chance of thromboembolism
- 1 MU = 600 mg

Adverse effects

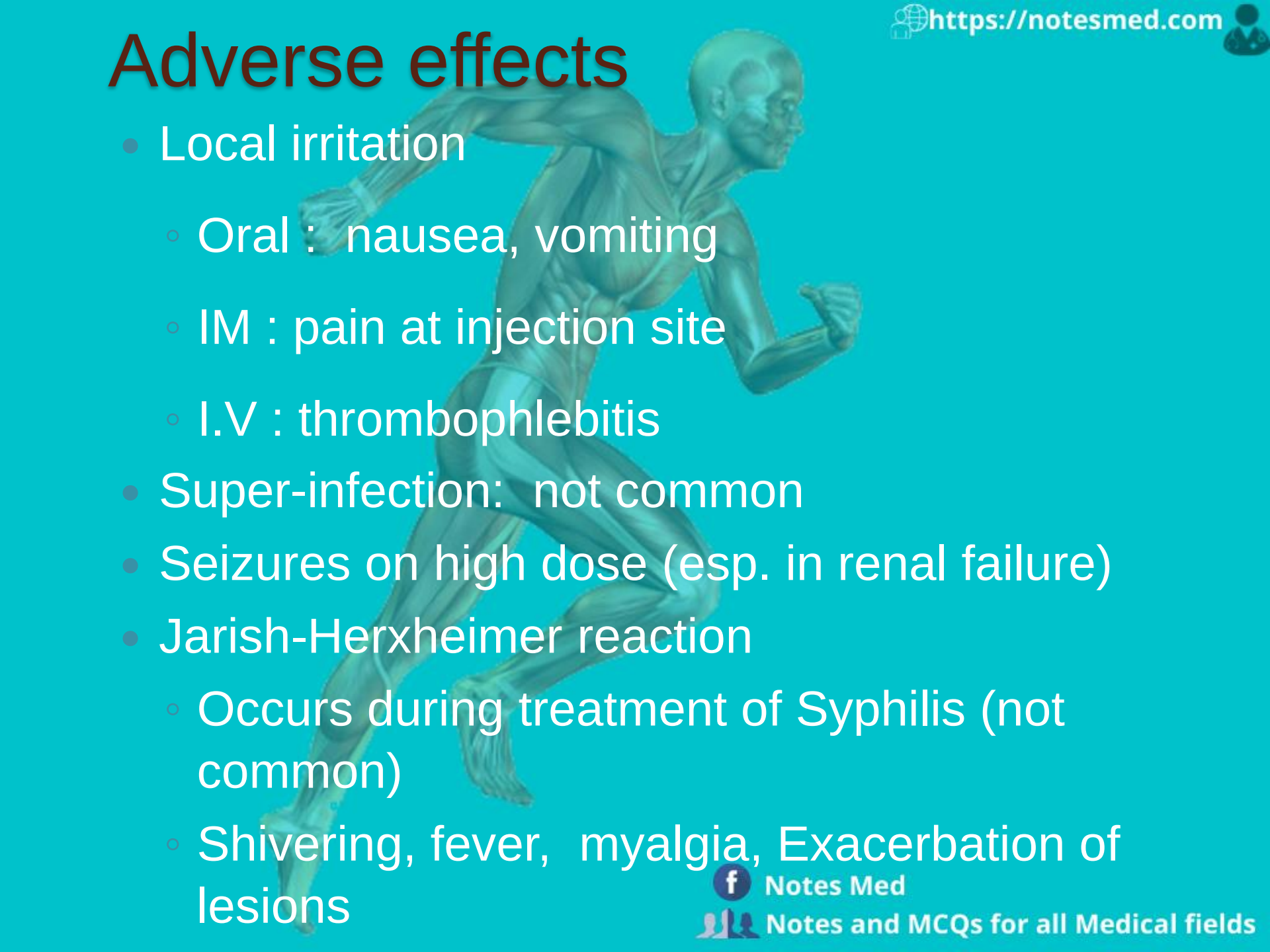
- Hypersensitivity
  - Rashes, itching, urticaria, fever, Dermatitis, bronchospasm, angioedema, joint pain, serum sickness or anaphylactic reaction.
  - Anaphylaxis (rare but may be fatal)
  - Cross sensitivity among :
    - Different types of penicillins
    - Other β-lactam antibiotics
    - Intradermal test before giving full dose : 2-10 IU





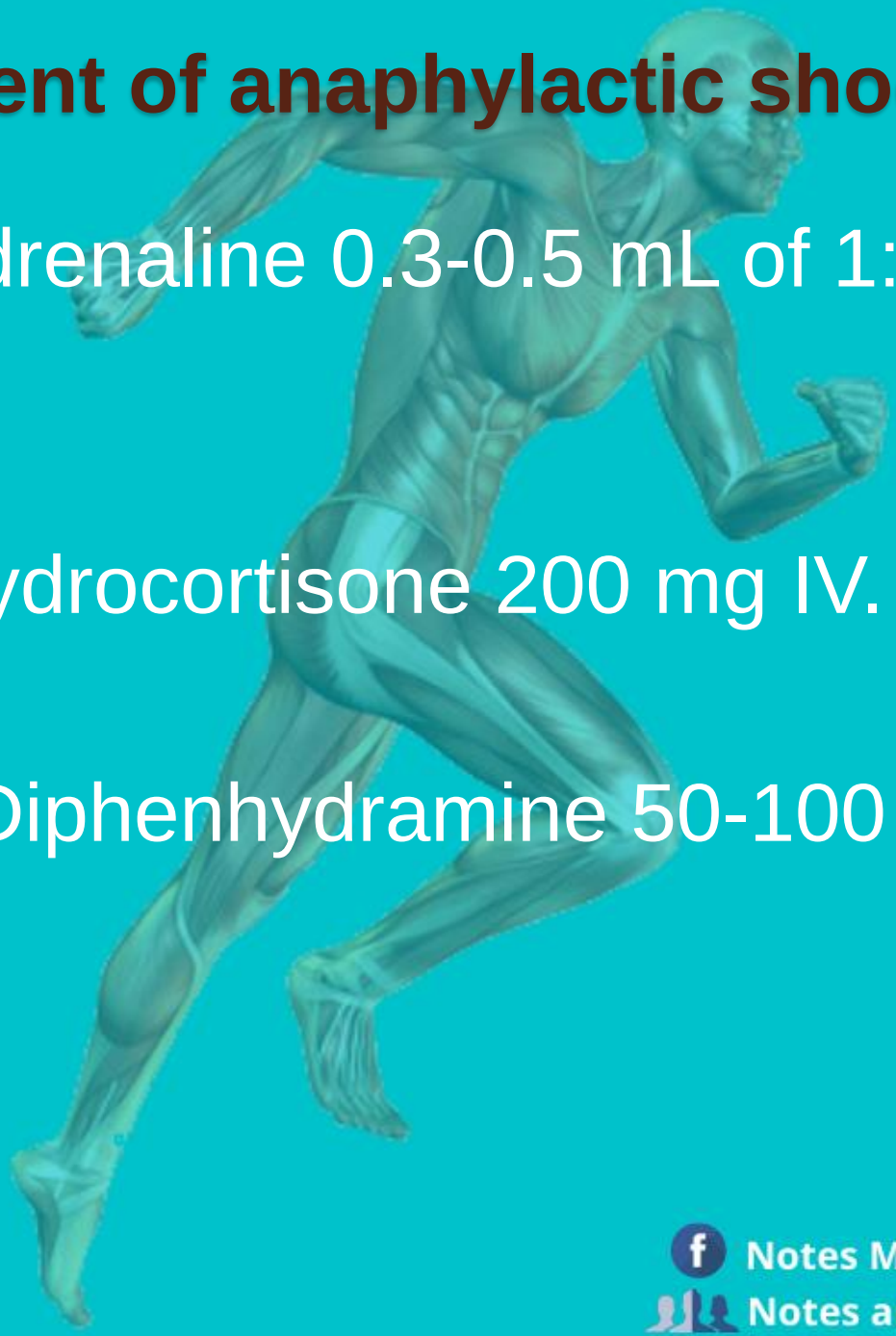


Adverse effects



- Local irritation
  - Oral : nausea, vomiting
  - IM : pain at injection site
  - I.V : thrombophlebitis
- Super-infection: not common
- Seizures on high dose (esp. in renal failure)
- Jarish-Herxheimer reaction
  - Occurs during treatment of Syphilis (not common)
  - Shivering, fever, myalgia, Exacerbation of lesions

Treatment of anaphylactic shock

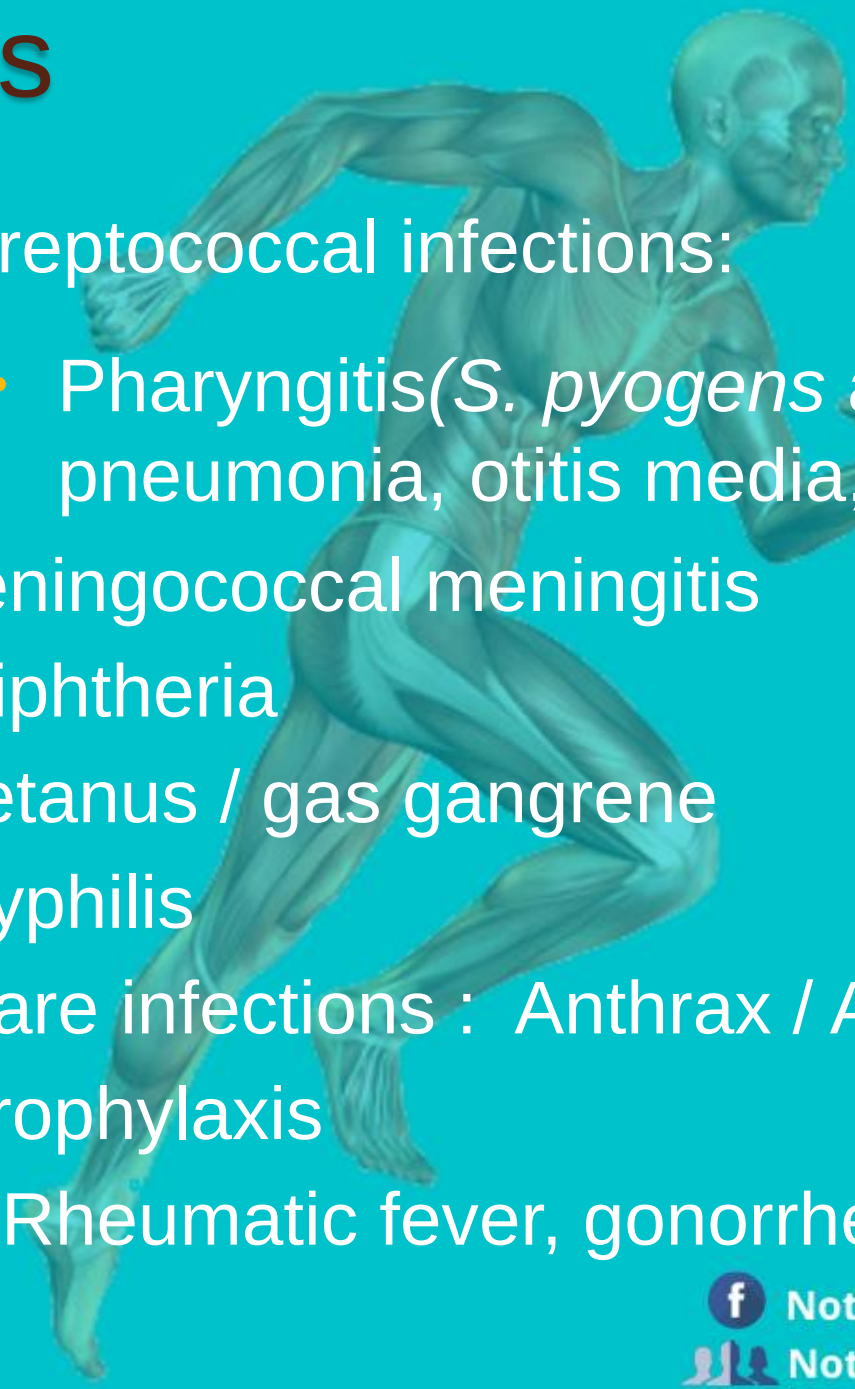


- Inj. Adrenaline 0.3-0.5 mL of 1:1000 solution IM.
- Inj. Hydrocortisone 200 mg IV.
- Inje. Diphenhydramine 50-100 mg IV or IM.

Precautions

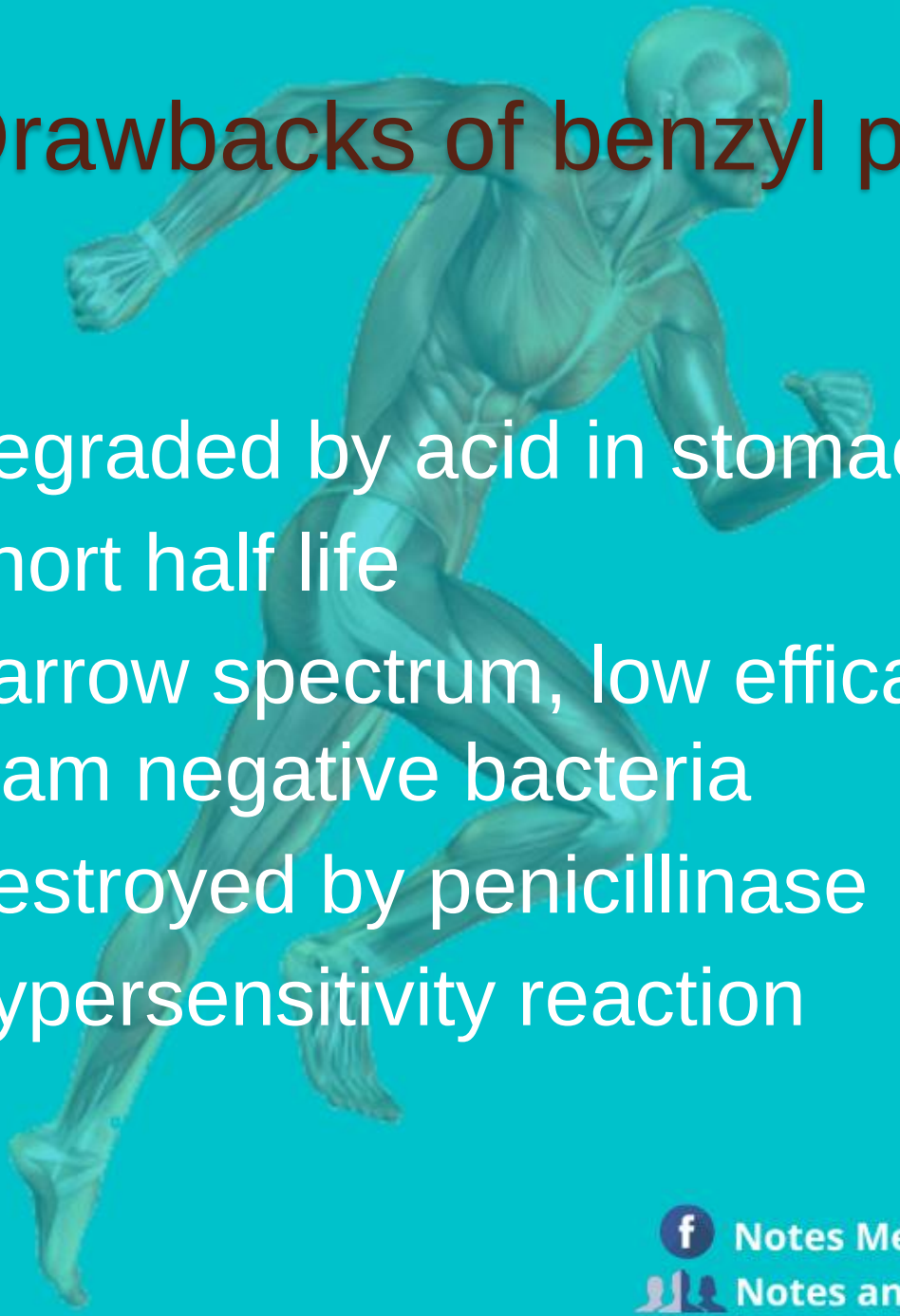
- Before giving penicillin, history of previous administration and allergic manifestations, if any, must be noted.
- In patients with history of asthma, allergic rhinitis, hay fever, etc., there is an increased risk of penicillin allergy, hence it should be avoided .
- Inj. Adrenaline and hydrocortisone should be kept ready before injecting penicillin to treat the anaphylactic reaction.
- Sensitivity test should be performed by intradermal test on the ventral aspect of forearm. Itching, erythema and wheal formation are observed. A negative skin test does not ensure absolute safety.

Uses



1. Streptococcal infections:
    - Pharyngitis(*S. pyogens* always sensitive), pneumonia, otitis media, meningitis
2. Meningococcal meningitis
3. Diphtheria
4. Tetanus / gas gangrene
5. Syphilis
6. Rare infections : Anthrax / Actinomycosis
7. Prophylaxis
    - Rheumatic fever, gonorrhea, endocarditis

Drawbacks of benzyl penicillin



- Degraded by acid in stomach
- Short half life
- Narrow spectrum, low efficacy against gram negative bacteria
- Destroyed by penicillinase
- Hypersensitivity reaction

Semi-synthetic Penicillins

- Acid-resistant penicillins
  - Phenoxymethyl penicillin (Penicillin V)
  - Aminopenicillins
- Penicillinase-resistant penicillins
  - (Methicillin) cloxacillin, flucloxacillin, dicloxacillin, nafcillin
- Extended-spectrum penicillins
  - Amino / Carboxy / Ureidopenicillins

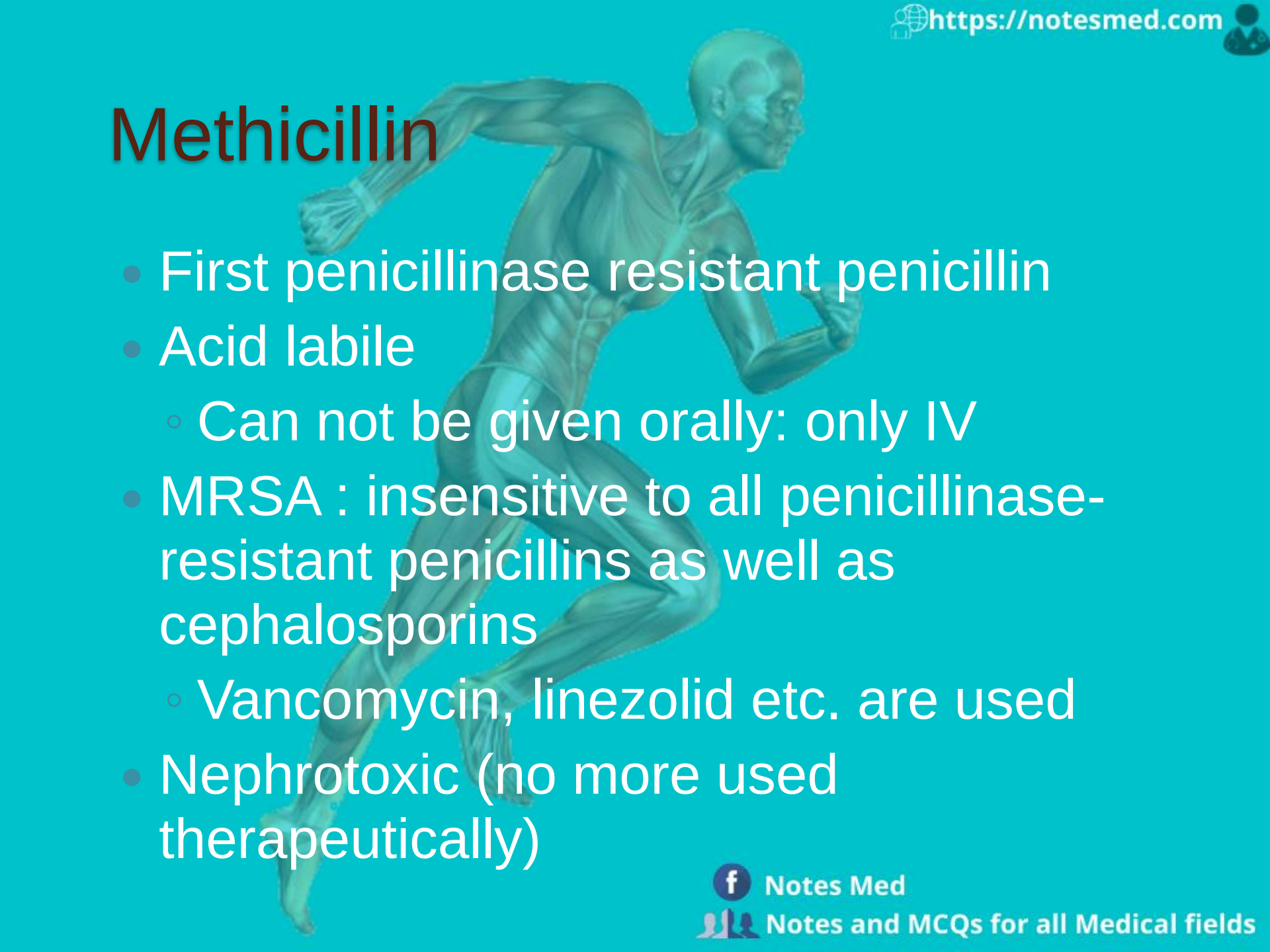
Phenoxy-methyl penicillin (Penicillin V)

- Semi-synthetic Penicillin
- Acid stable
  - Can be given orally
- Efficacy slightly lower than Penicillin G
  - Esp. for Neisseria and Gram –ve bacteria
  - Used only for non severe infections like streptococcal pharyngitis and prophylaxis

Penicillinase-resistant penicillins

- Methicillin: no more used clinically
- Cloxacillin / flucloxacillin, dicloxacillin, nafcillin : **oral and/or parenteral**
- **Relatively stable in acidic medium , absorbed adequately after oral administration (30-80%)**
- **Absorption is more when taken on an empty stomach**
- Efficacy lower than penicillin G for penicillin sensitive bacteria

Methicillin

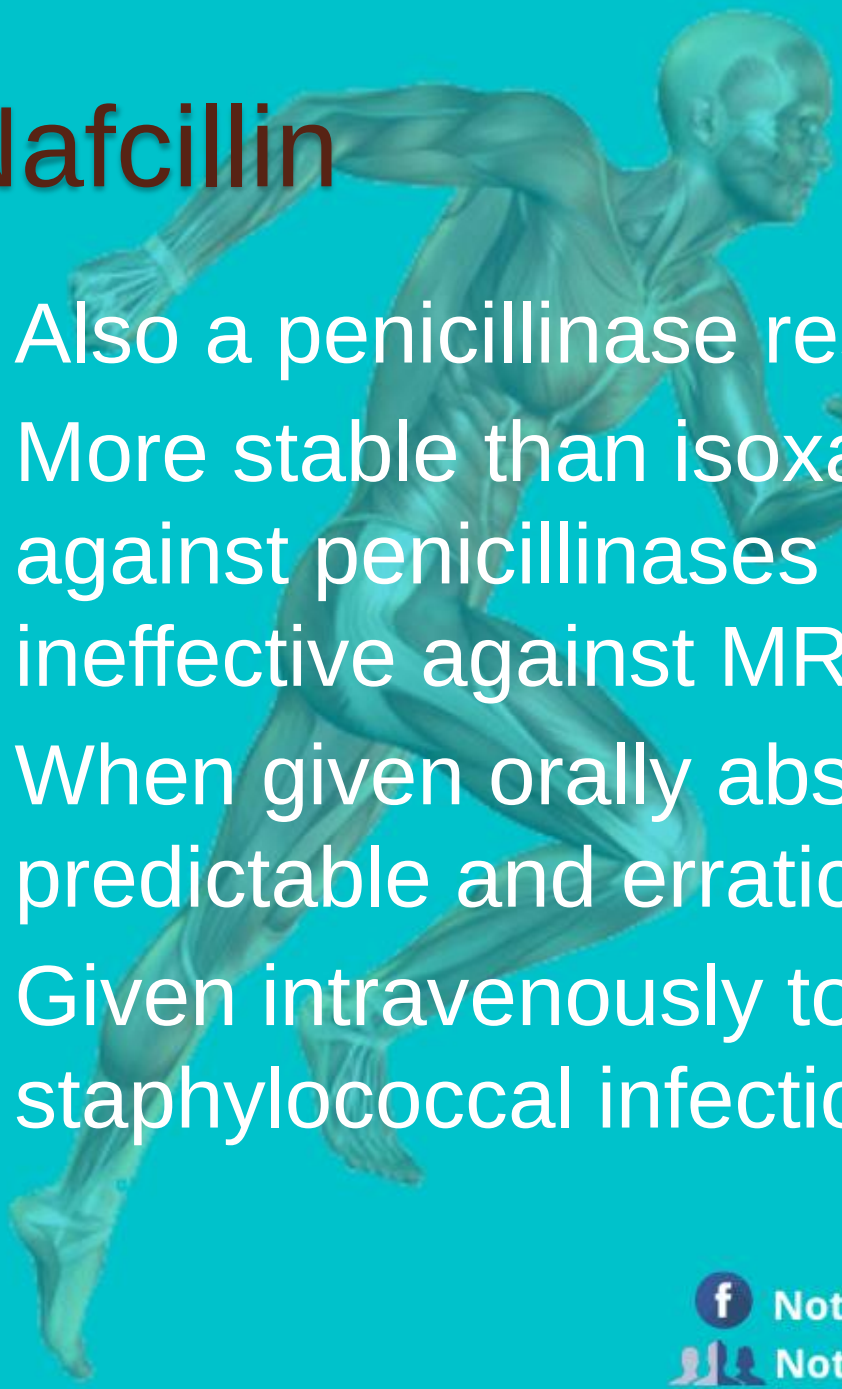


- First penicillinase resistant penicillin
- Acid labile
  - Can not be given orally: only IV
- MRSA : insensitive to all penicillinase-resistant penicillins as well as cephalosporins
  - Vancomycin, linezolid etc. are used
- Nephrotoxic (no more used therapeutically)

Cloxacillin / Flucloxacillin

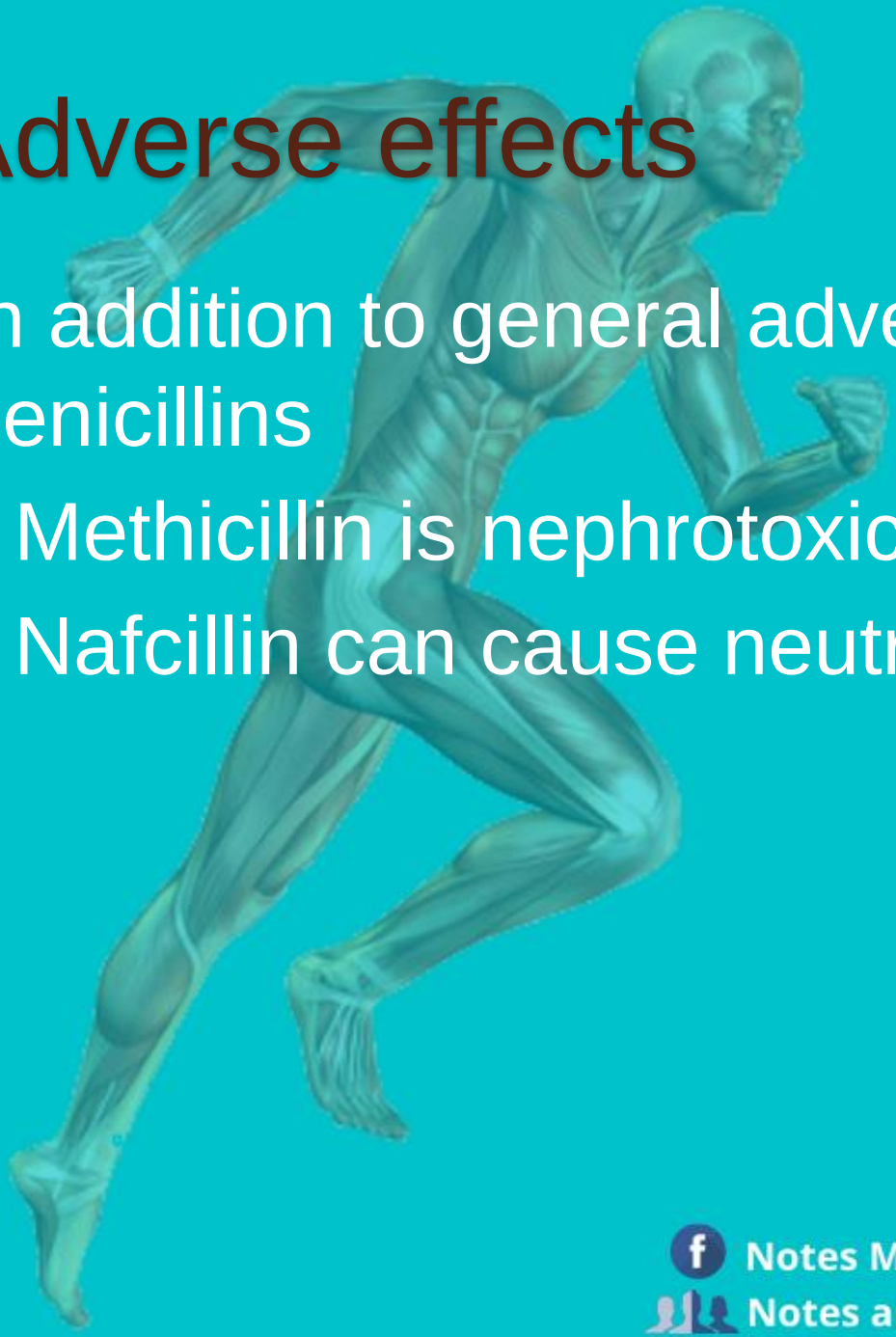
- Acid resistant and resistant to penicillinases
- Lower activity against penicillin G sensitive organisms
  - should not be used as a substitute
- Not effective against MRSA
- Flucloxacillin better absorbed when given orally and has longer $t_{1/2}$

Nafcillin



- Also a penicillinase resistant penicillin
- More stable than isoxazolyl penicillins against penicillinases but equally ineffective against MRSA
- When given orally absorption is not predictable and erratic
- Given intravenously to treat systemic staphylococcal infections

Adverse effects



In addition to general adverse effects of penicillins

- Methicillin is nephrotoxic
- Nafcillin can cause neutropenia

Aminopenicillins

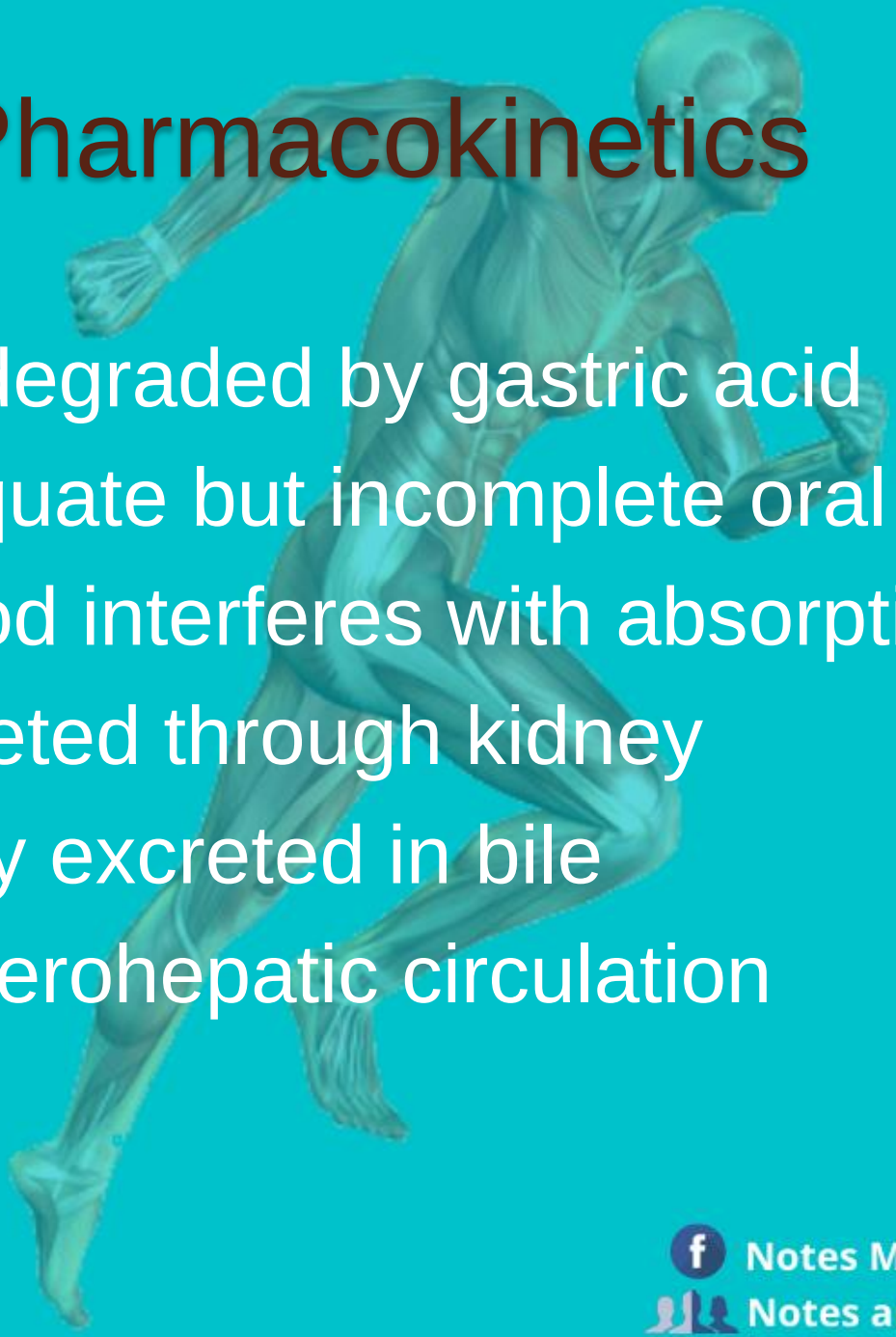
- Amino substitution in the side chain
- Oral absorption is reliable
- Commonly used penicillins
- All have similar antibacterial effects
  - Destroyed by penicillinases
- Drugs:
  - Ampicillin
  - Amoxicillin

Ampicillin

Extended spectrum:

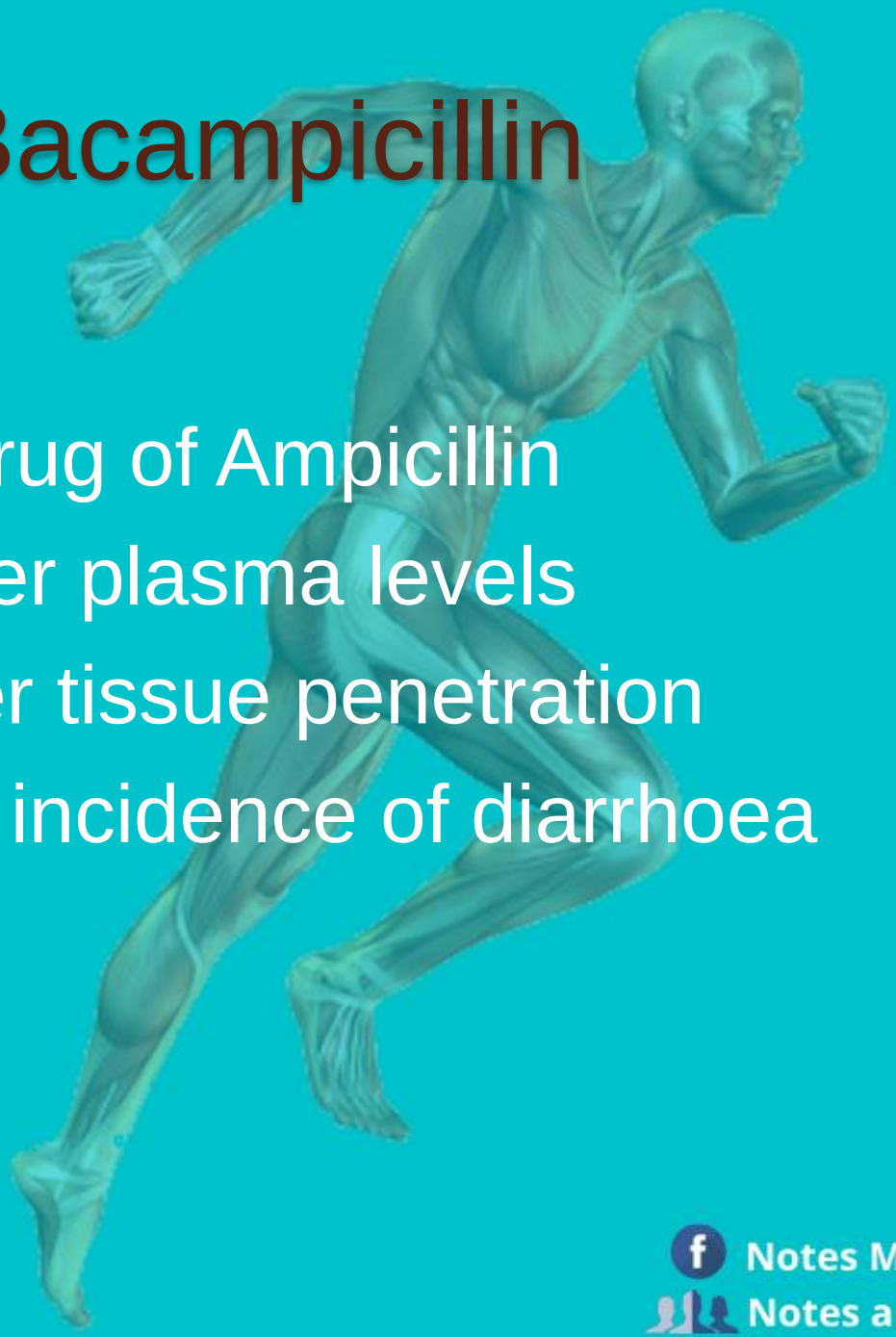
- Gram + ve bacteria and some additional gram –ve bacteria:
  - *H. influenzae, E. Coli, Proteus*,
  - *Salmonella, Shigella*
  - *Streptococcus viridans* and *enterococci*
    - No effect on *Pseudomonas, Klebsiella or Bacteroids*

Pharmacokinetics



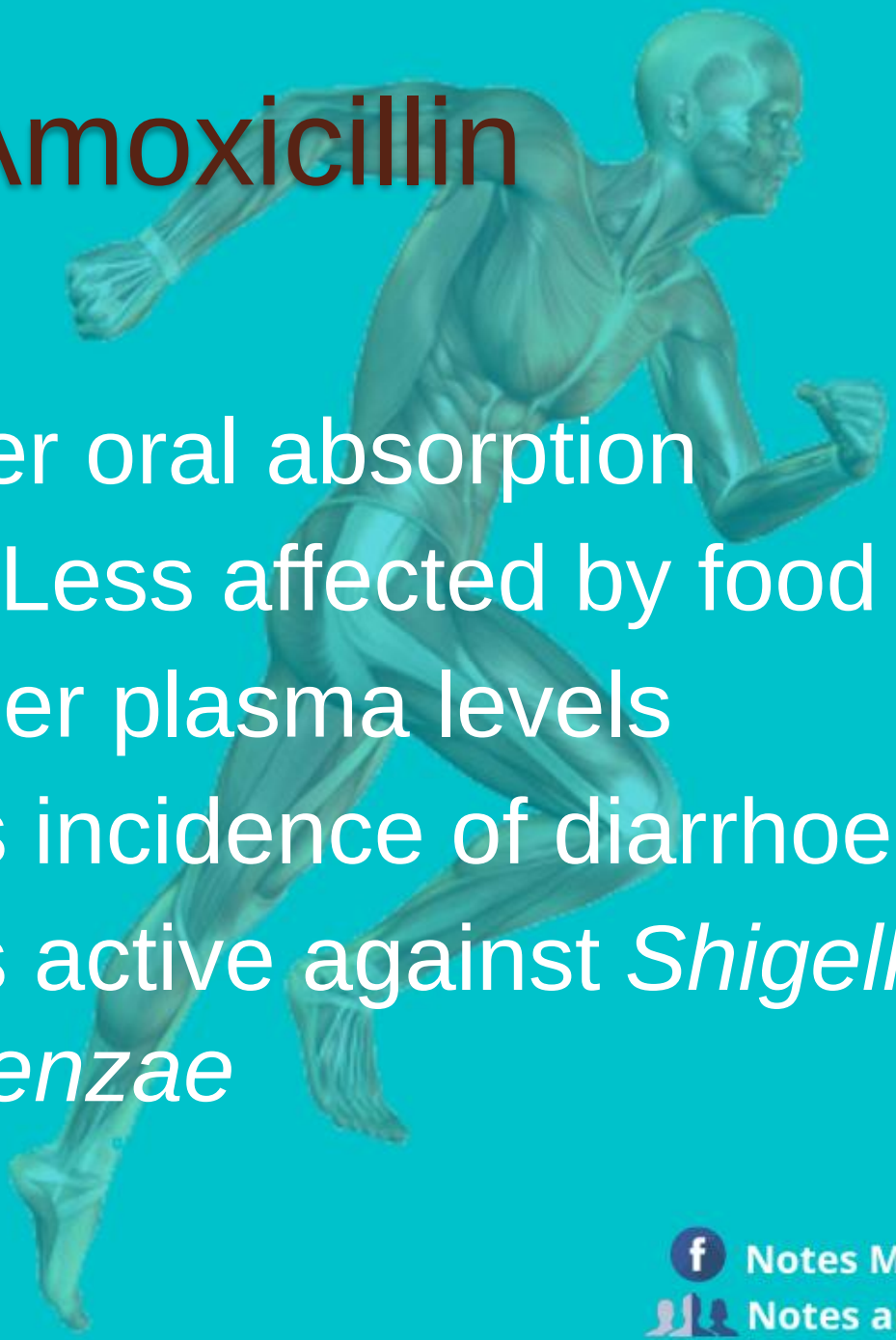
- Not degraded by gastric acid
- Adequate but incomplete oral absorption
  - Food interferes with absorption
- Excreted through kidney
- Partly excreted in bile
  - Enterohepatic circulation

Bacampicillin



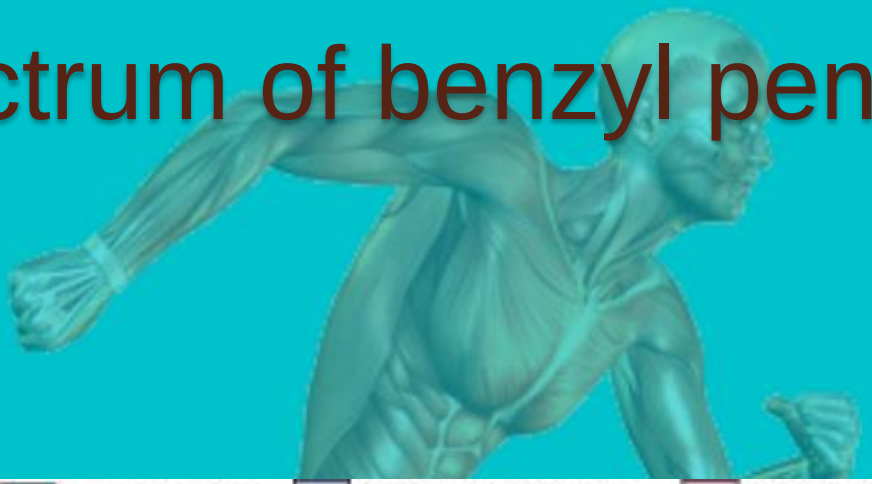
- Prodrug of Ampicillin
- Higher plasma levels
- Better tissue penetration
- Less incidence of diarrhoea

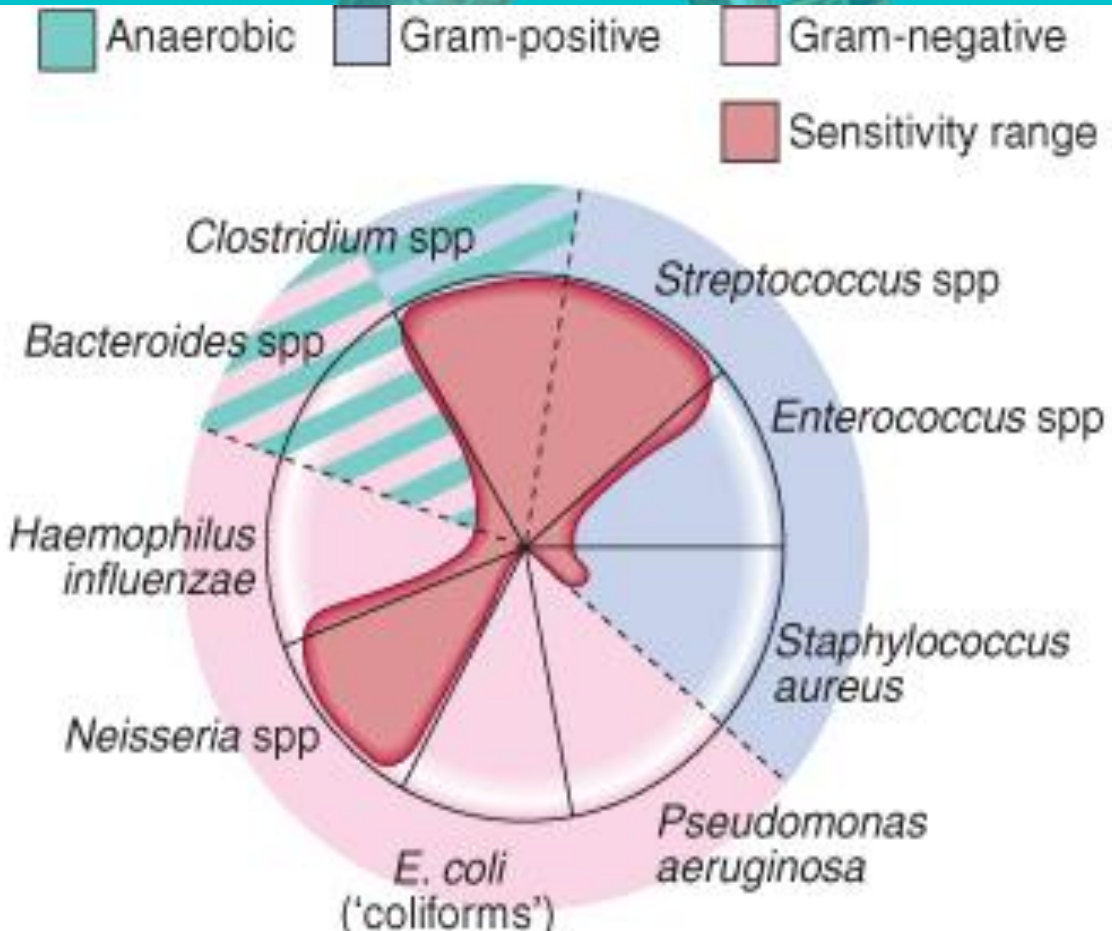
Amoxicillin



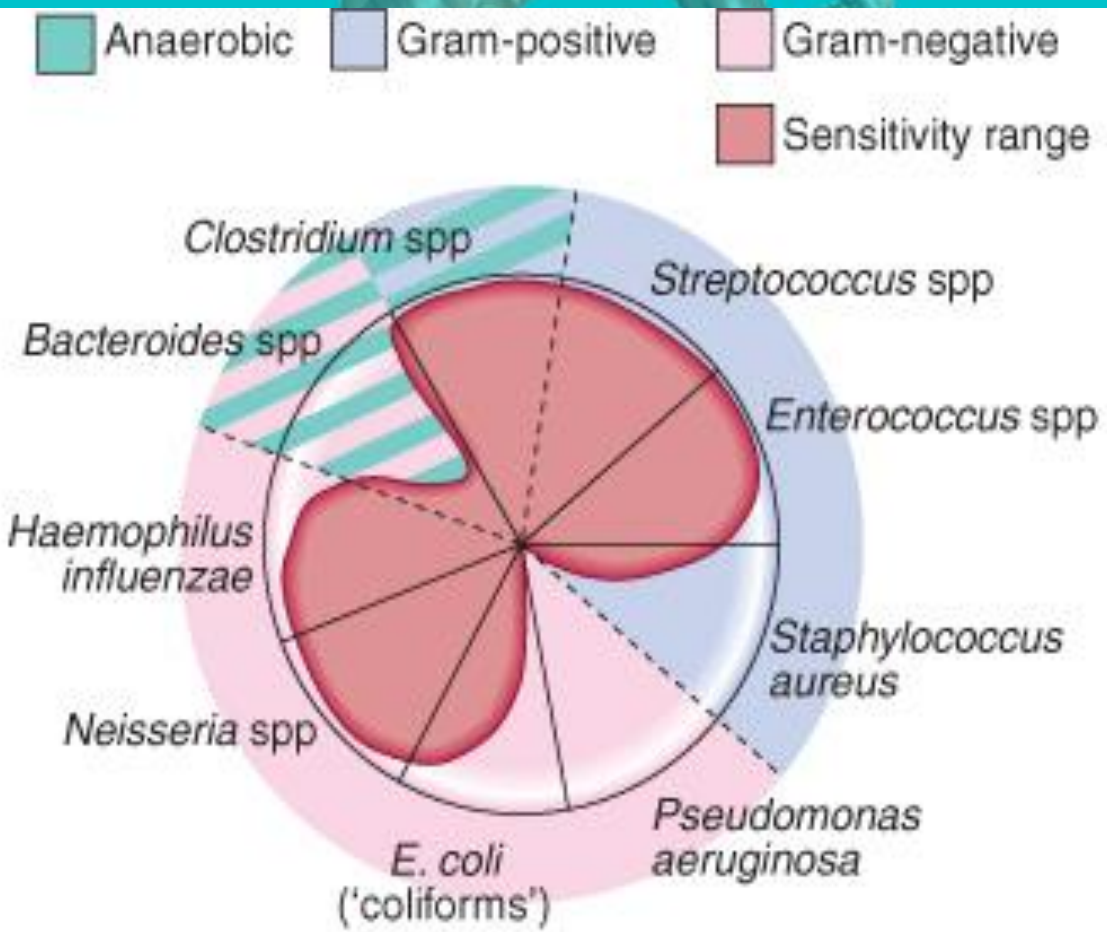
- Better oral absorption
  - Less affected by food
- Higher plasma levels
- Less incidence of diarrhoea
- Less active against *Shigella & H. influenzae*

Spectrum of benzyl penicillin





Spectrum of aminopenicillins

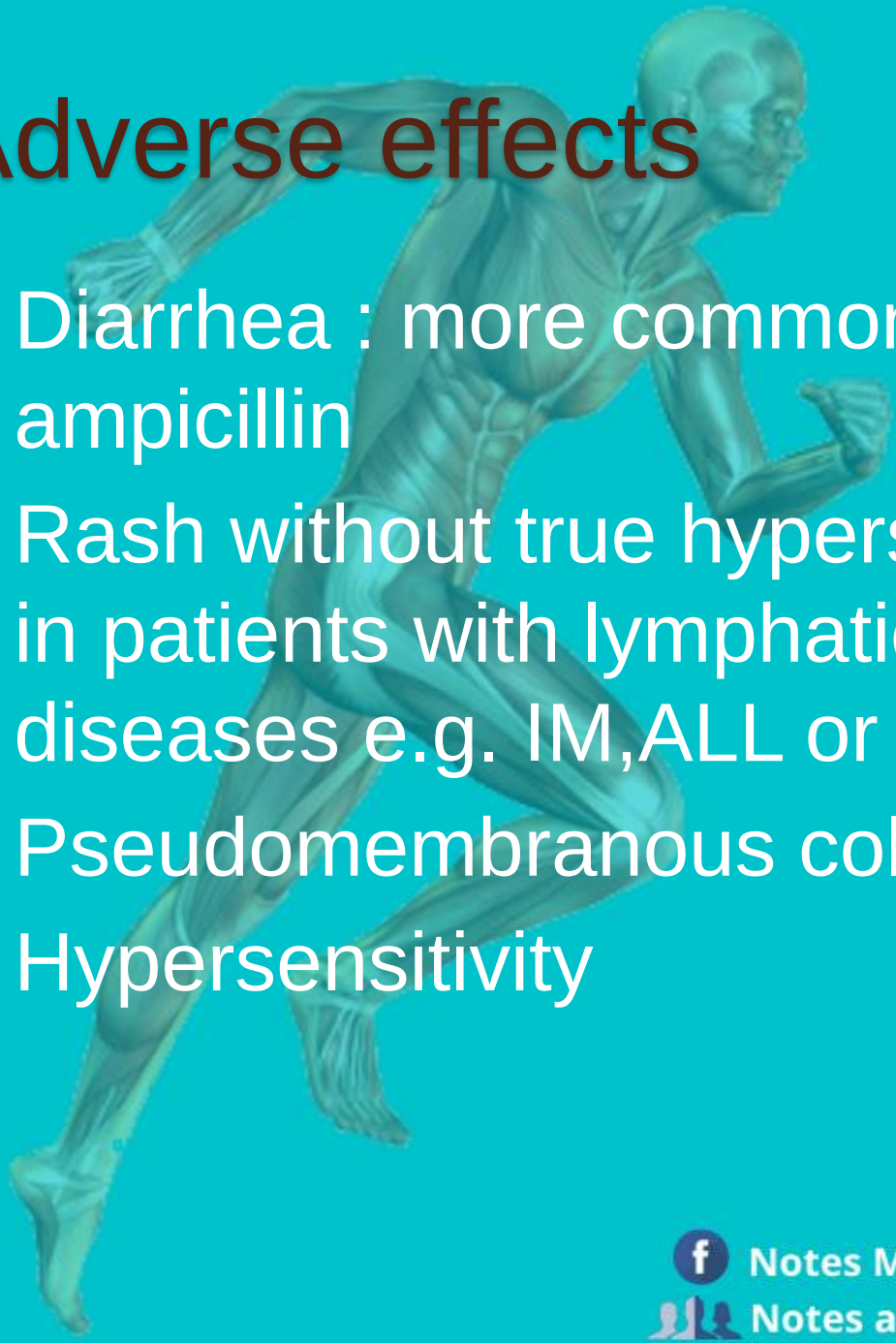


Uses

1. Respiratory tract infections
2. Urinary tract infection in pregnancy
3. Meningitis due to listeria and *H. influenzae*
4. SABE
5. Typhoid, dysentery, cholecystitis
6. Mixed infections or empirical treatment of severe infections in combination with other antimicrobial

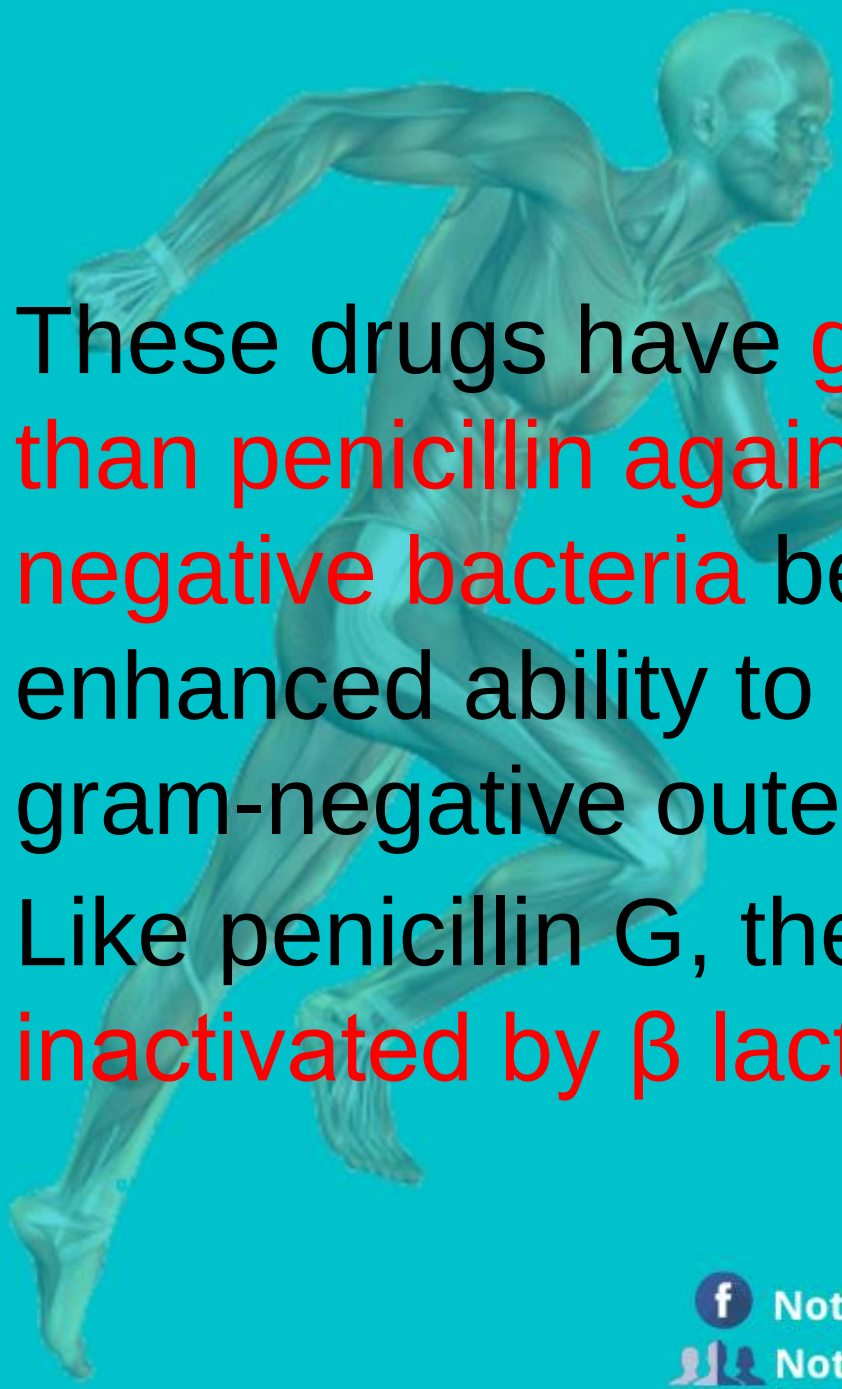
Adverse effects

- Diarrhea : more common with ampicillin
- Rash without true hypersensitivity esp. in patients with lymphatic system diseases e.g. IM,ALL or renal failure
- Pseudomembranous colitis
- Hypersensitivity



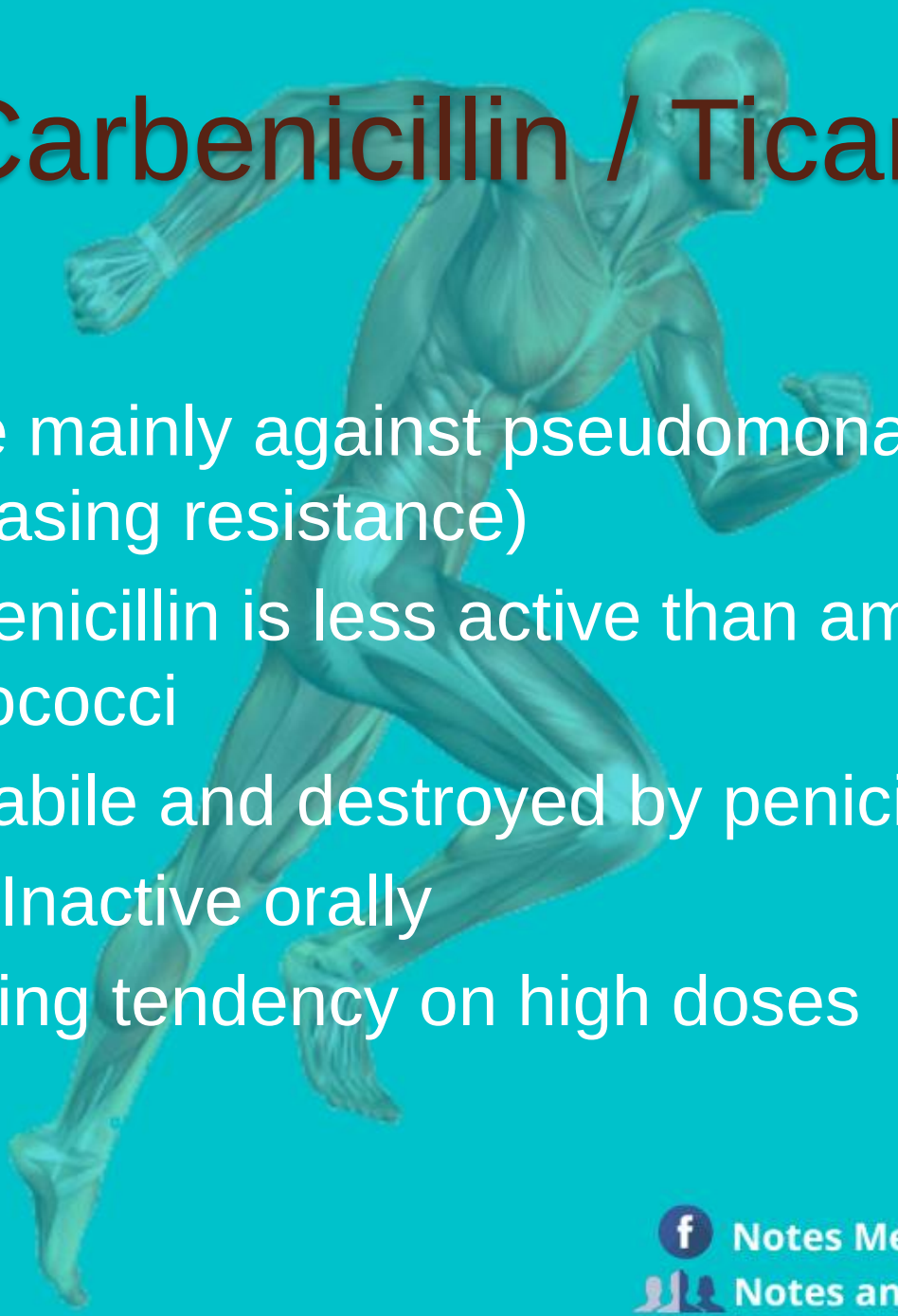
Anti-pseudomonal penicillins

- Carboxypenicillins
  - Carbenicillin / Ticarcillin
- Ureidopenicillin
  - Piperacillin



- These drugs have greater activity than penicillin against many gram negative bacteria because of their enhanced ability to penetrate the gram-negative outer membrane.
- Like penicillin G, they are inactivated by β lactamases

Carbenicillin / Ticarcillin

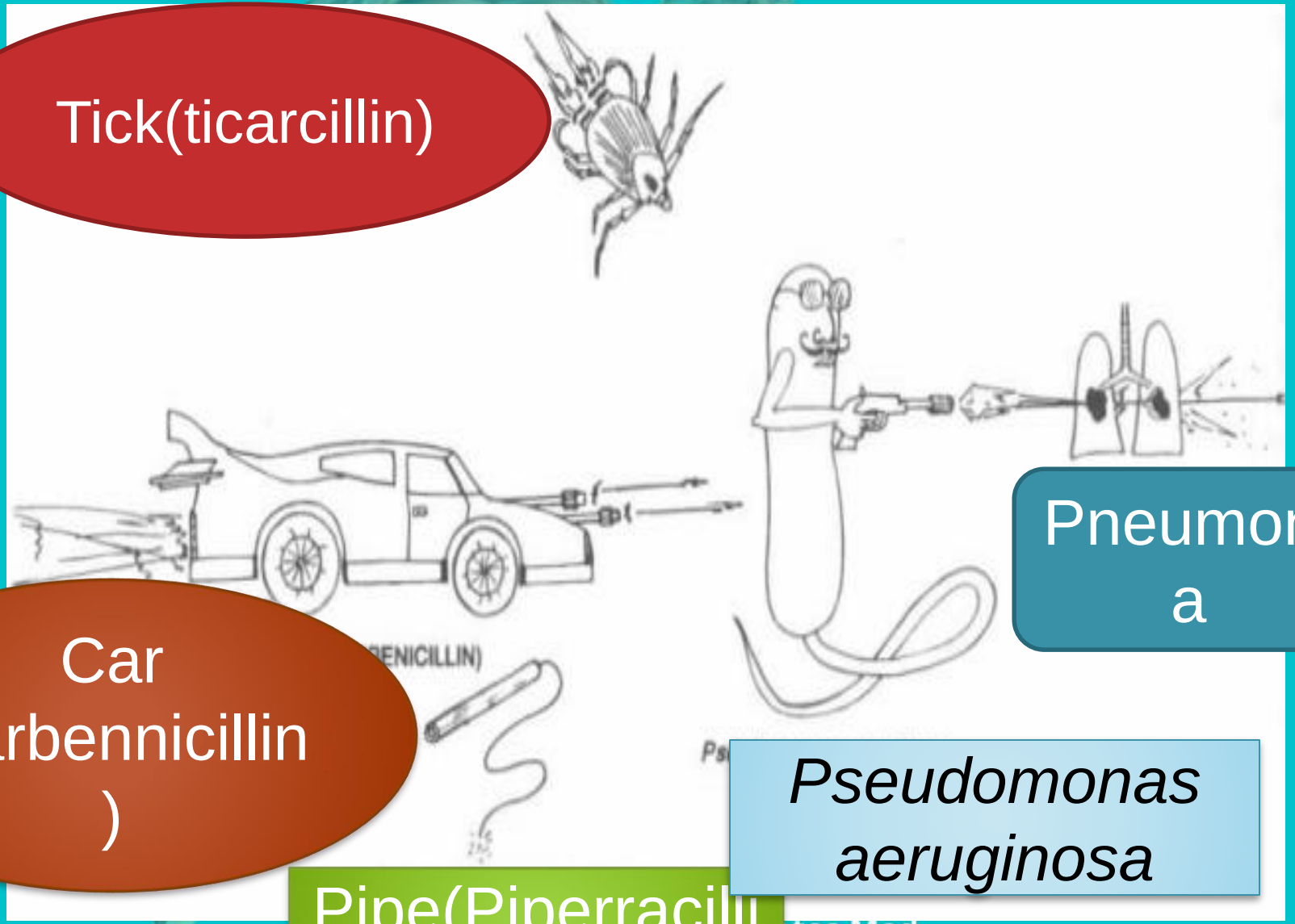


- Active mainly against pseudomonas and proteus (increasing resistance)
- Carbenicillin is less active than ampicillin against enterococci
- Acid labile and destroyed by penicillinases
  - Inactive orally
- Bleeding tendency on high doses

Anti-pseudomonal penicillins

- Ticarcillin
  - More potent and less adverse effects
- Piperacillin
  - 8 times more potent than carbenicillin
  - Crosses BBB
  - Good activity against klebsiella also
  - Used mainly in systemic pseudomonas infections usually with a second AMA

Tick(ticarcillin)



Pneumonia

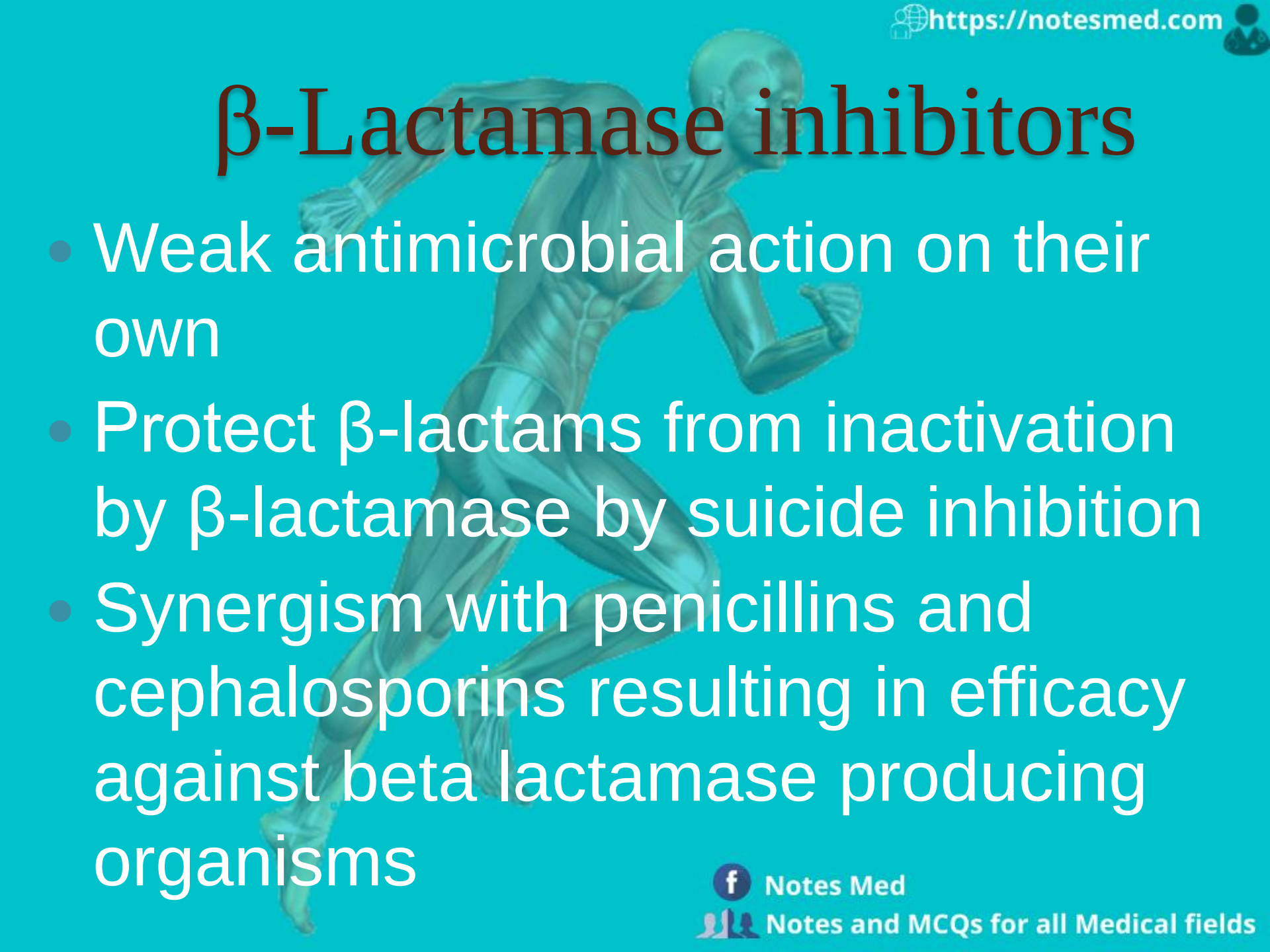
Car (carbennicillin)

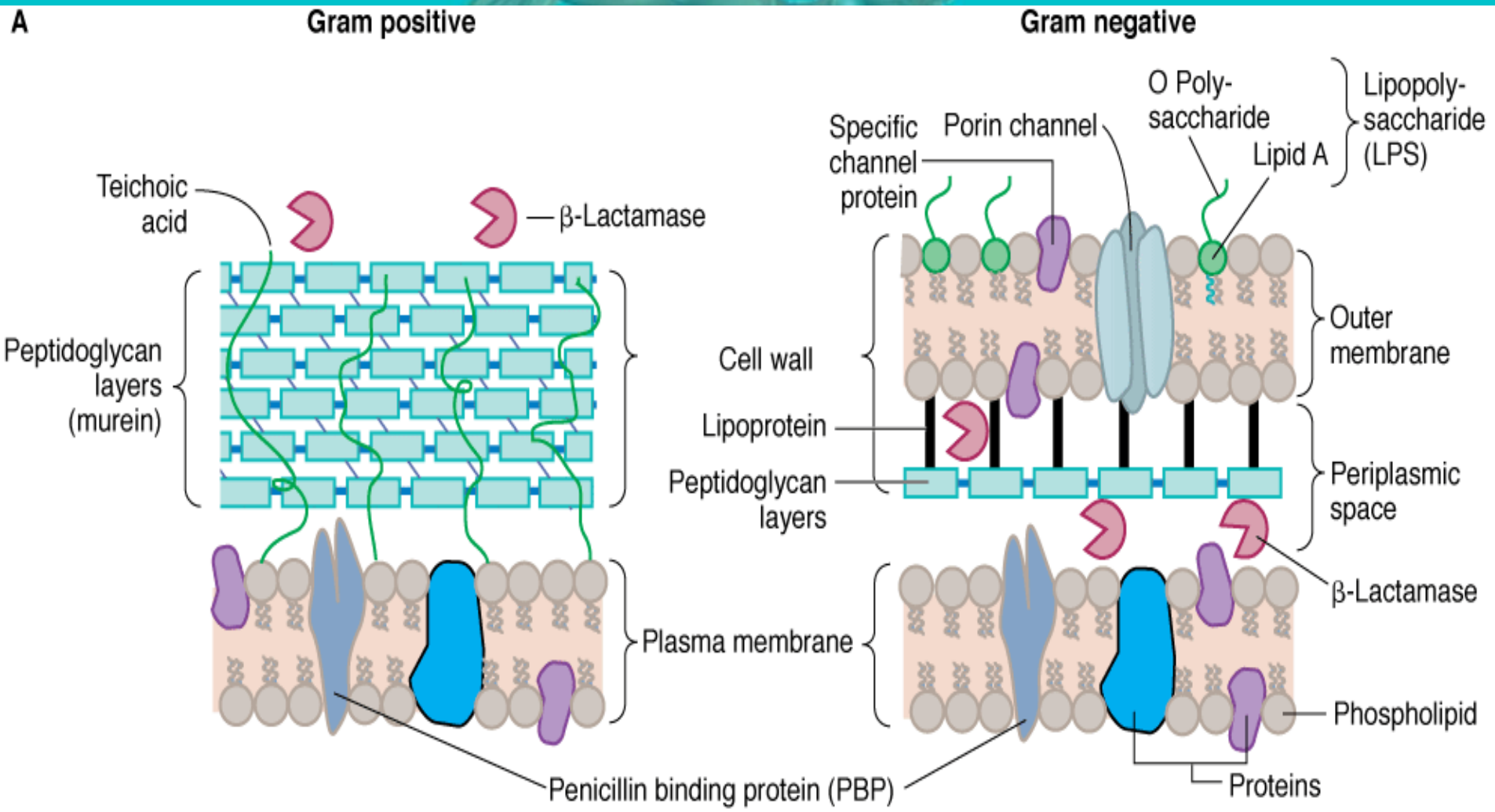
Pseudomonas aeruginosa

Pipe(Piperracillin)

β-Lactamase inhibitors

- Weak antimicrobial action on their own
- Protect β-lactams from inactivation by β-lactamase by suicide inhibition
- Synergism with penicillins and cephalosporins resulting in efficacy against beta lactamase producing organisms





β-Lactamase inhibitors

- **Clavulanic acid**
  - With amoxicillin (or ticarcillin, cephalosporins)
    - For respiratory tract and soft tissue infections, gonorrhea etc.
- **Sulbactam**
  - With ampicillin For gonorrhea due to PPNG and mixed aerobic-anaerobic infections
- **Tazobactam**
  - With piperacillin
  - For severe GI, respiratory or urinary tract infections due to gram negative bacteria mostly in combination with other AMAs