抗 生 素 簡 介

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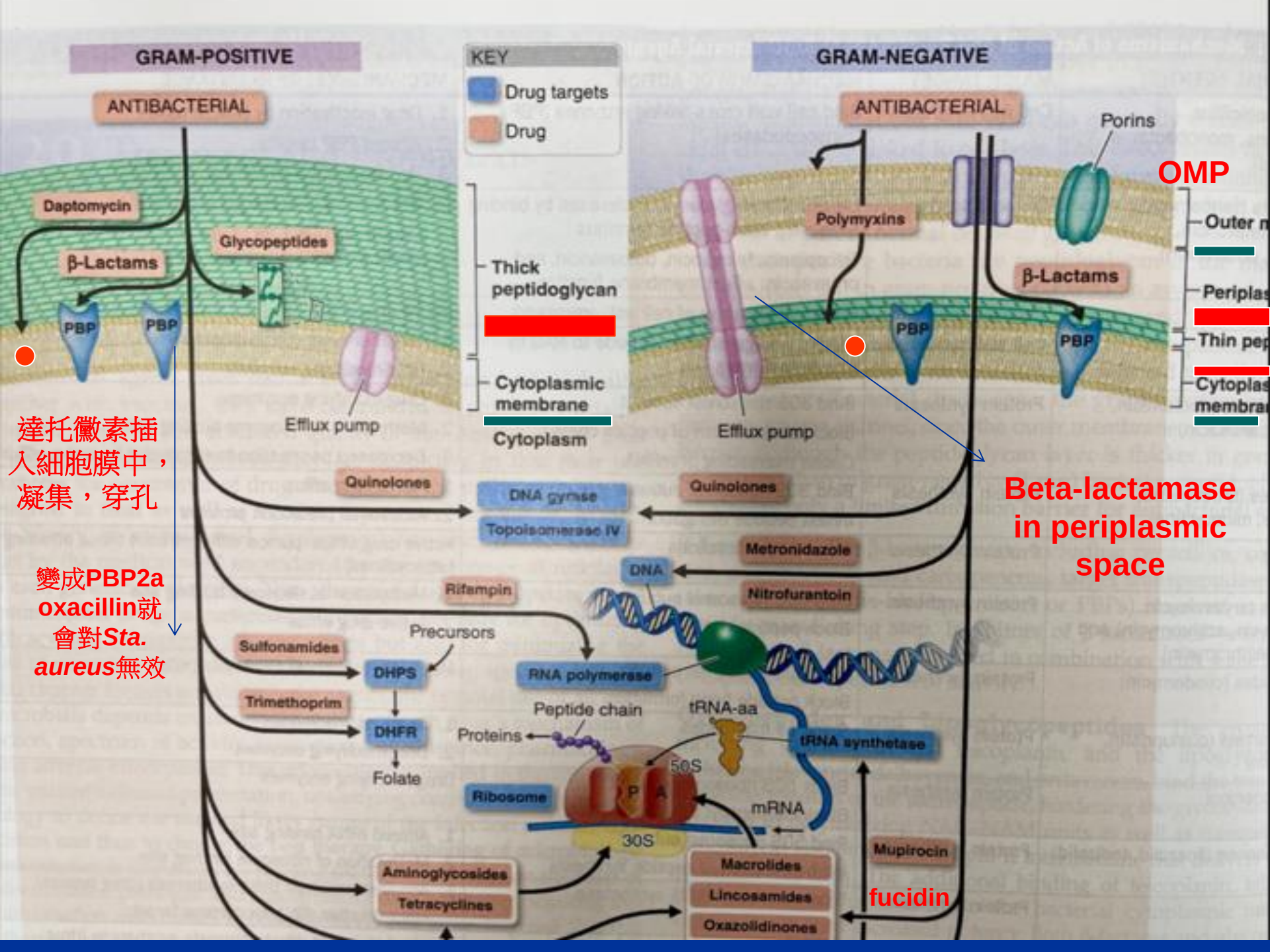
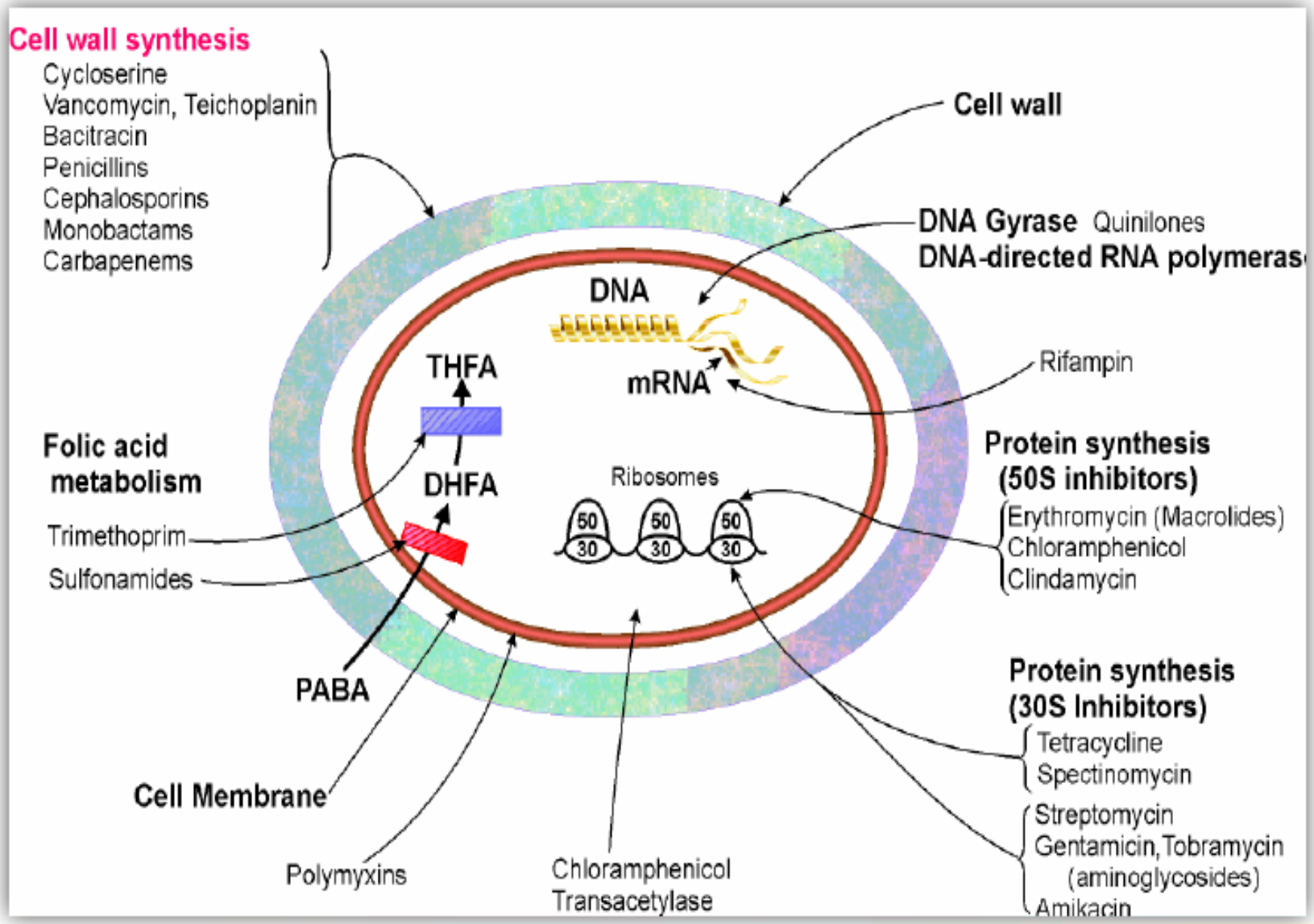
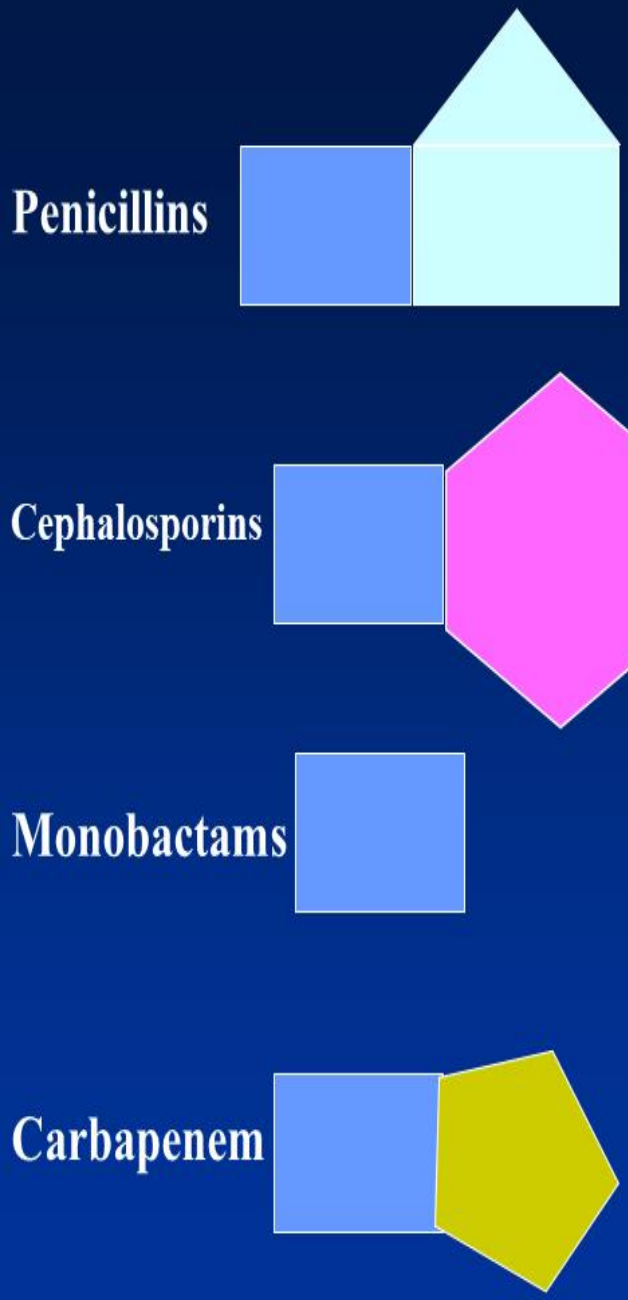
Classes of Antibacterial Agents

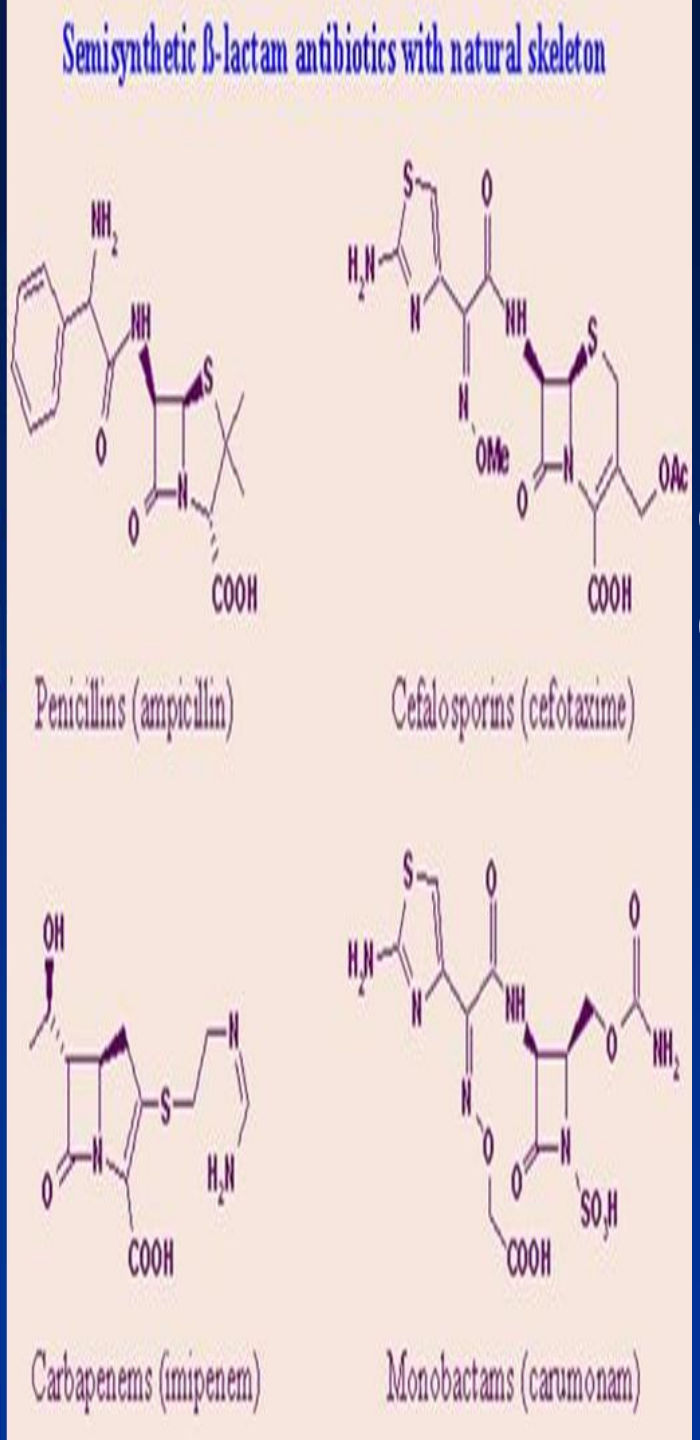
- β-Lactams
- Penicillins
- Cephalosporins
- Carbapenem
- Aminoglycosides
- Glycopeptides
- Oxazolidinones
- Quinolones
- Sulfamethoxazole/Trimethoprim
- Clindamycin
- Metronidazole
- Tigecycline
- Colistin
- Minocycline
- Daptomycin
- Echinocandins(抗黴)


GRAM-POSITIVE
KEY
Drug targets
Drug
GRAM-NEGATIVE
ANTIBACTERIAL
ANTIBACTERIAL
Porins
OMP
Daptomycin
Glycopeptides
β-Lactams
Polymyxins
β-Lactams
PBP
PBP
PBP
PBP
Thick peptidoglycan
Cytoplasmic membrane
Cytoplasm
Efflux pump
Efflux pump
Outer m
Periplas
Thin pep
Cytoplas
membra
達托黴素插入細胞膜中，凝集，穿孔
變成PBP2a oxacillin就會對Sta. aureus無效
Quinolones
DNA gyrase
Topoisomerase IV
Quinolones
Beta-lactamase in periplasmic space
Metronidazole
DNA
Rifampin
Nitrofurantoin
Precursors
Sulfonamides
DHPS
RNA polymerase
Trimethoprim
DHFR
Peptide chain
tRNA-aa
Proteins
tRNA synthetase
Folate
50S
Ribosome
P
A
mRNA
30S
Mupirocin
Aminoglycosides
Tetracyclines
Macrolides
Lincosamides
Oxazolidinones
fucidin

Classification of Antibiotics







- β-Lactams

Penicillins
Cephalosporins
Carbapenems

Penicillins

- Natural Penicillin
  - Aqueous penicillin G
  - Benzathine penicillin G
- Penicillinase-resistant penicillins
  - Oxacillin
  - Dicloxacillin
- Aminopenicillin
  - Ampicillin
  - Amoxicillin

Ureidopenicillins

- Piperacillin
- Penicillin + β -lactamase inhibitors
  - Amoxicillin/clavulanate
  - Ampicillin/sulbactam
  - Piperacillin/tazobactam
  - cefoperazone-/sulbactam
  - Ceftazidime/avibactam
  - Ceftolozane-tazobactam

Penicillins

作用機轉：抑制細胞壁之合成殺菌作用 (bactericidal)

- Natural penicillin
- Aminopenicillin
- Antistaphylococcal penicillin
- Antipseudomonal penicillin

- Natural penicillin
- Aqueous penicillin G (benzylpenicillin)
- Benzathine penicillin G

抗菌譜: *Streptococci*、*Pneumococci*
Meningococci、
Leptospira、*Treponemes* 、
Actinomyces
Anaerobes, e.g. *Fusobacteria*
Peptococci

副作用：過敏性反應（皮疹、發燒、過敏性休克）
神經性毒性（seizure）
腎臟毒性（nephritis）
血液毒性（hemolytic anemia）
血清電解質異常

- Penicillinase-resistant PCN (Antistaphylococcal PCN)

Oxacillin (IV) – Prostaphyllin

Dicloxacillin (PO)

- Staphyloccoccal infections – OSSA, OSSE

適應症：骨髓炎、皮膚及軟組織發炎、　　註：腎功能異常患者不需調整劑量

- Side effects: neutropenia, hepatitis, diarrhea

- Aminopenicillins - Ampicillin, Amoxicillin
- Active against enterococci, *H. influenzae(*beta-lactamase (-)*)*, *E. coli, Proteus mirabilis, Salmonella spp., Shigella spp.* Anaerobes（*B. fragilis* 除外）
- Oral absorption rate: 50% vs. 90%
- Indication:
  - Acute otitis media
  - Acute sinusitis
-

Antipseudomonal penicillin

Ureidopenicillins

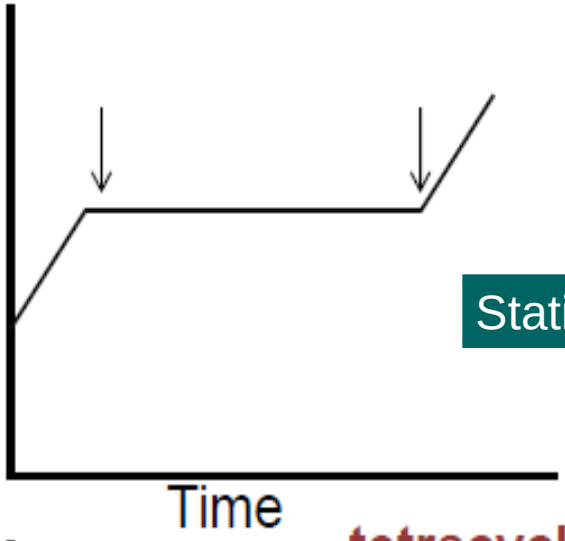
- Piperacillin

抗菌譜: *Pseudomonas* 及
indole-positive *Proteus*

註： 治療*Pseudomonas aeruginosa*
與aminoglycoside合併使用增加療效

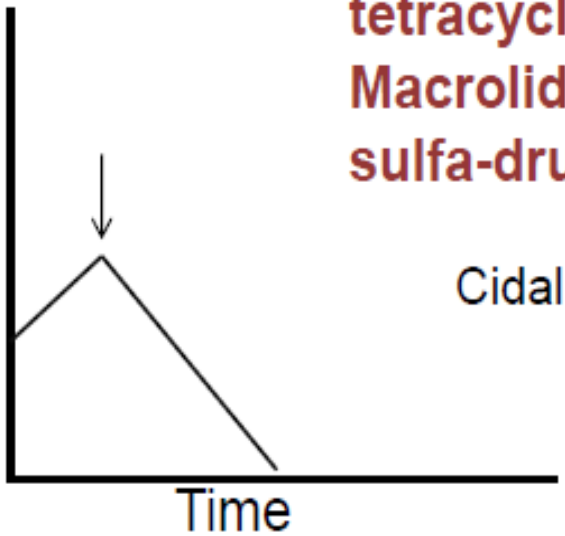
- Not good effect to *E.coli*
- Activity against streptococci, enterococci, anaerobes

Bactericidal & Bacteriostatic



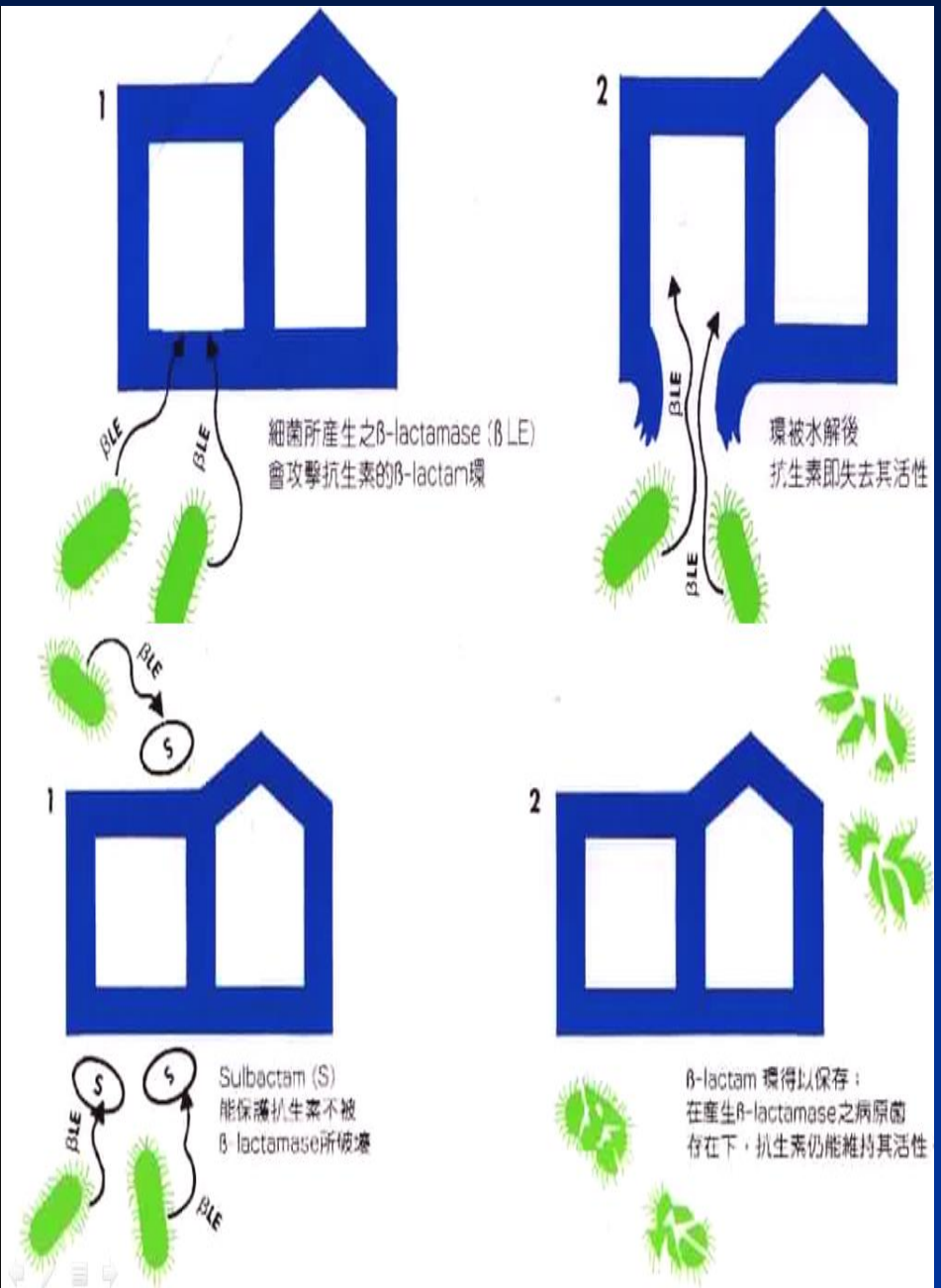
Static drug → Suppression of the duplication, but recovery after removal of agent

tetracyclines
Macrolides, clindamycin
sulfa-drug, linezolid



Cidal drug → Kill the cell

Beta-lactamase inhibitors



Clavulanate, Sulbactam, Tazobactam,avibactam

- + amoxicillin, ampicillin, piperacillin,cefaperazone, ceftazidime
- Augmentin, Unasyn, Tazocin,brosym,zavicefta
- Mechanisms of action
- Not penetrate BBB
- Effective to OSSA, *H. influenzae, M. catarrhalis, B. fragilis*
- Ineffective to bacteria those produce Amp C β-lactamase

Amp C β-lactamase

- Inducible and derepressed (constitutive)
- Gene is located in chromosome of bacteria including:
  Enterobacter cloacae
  Serratia marcescens
  Citrobacter freundiii
  Acinitobacter baumannii
  Pseudomonas aeruginosa
  Morganella morganii
  Proteus vulgaris

- Inducible:因為Amp C β-lactamase量不多 in vitro敏感性試驗可能呈S, 可用piperacillin 治療輕微感染
- Bacteremia or pneumonia: treatment with 4th generation Cephalosporins, carbapenem ,aminoglycoside, quinolone
- Derepressed: treatment with 4th generation Cephalosporins,carbapenem, aminoglycoside, quinolone

ESBL(extended spectrum β-lactamase)

- TEM-3,SHV-2,OXA,CTX-M 最常見基因型
- 2016研究 more than 150 types
- Mainaly in Enterobacteriaceae spp.:
- –*Escherichia coli*
- –*Klebsiella* spp.
- –*Proteus mirabilis*
- –*Salmonella* spp
- - ESBL- *K. p* : 26%
- - ESBL- *E. coli* : 23%
- Treatment recommendation: 輕至中度感染用 cephamycin ,重度感染用Carbapenem

Cephalosporins

- Loosely grouped into "generations" based on their spectrum of activities
- 5 generations
- Inhibit bacterial cell wall synthesis
- All cephalosporins ineffective to enterococci

1st generation Cephalosporins

- Cefazolin (1–2 g IV/IM q8h)
- cephradine (1–2 g IV/IM q4–6h)

Indication:

- staphylococci, streptococci
- community-acquired *Escherichia coli*, *Klebsiella*, and *Proteus* species

註：無法穿透至腦脊髓液中

2nd generation cephalosporins

2 groups: true cephalosporin, synthetic cephamycins

- Cefamandole, cefuroxime,
- Enhanced gram-negative activities, maintaining gram-positive activities
- Cefoxitin, cefmetazole: more anaerobic activities

3rd generation Cephalosporins

- Most gram-negative organisms
- Nosocomial infections
- Cefotaxime(半衰期最短）
- Ceftriaxone(半衰期最長）
- Ceftazidime-- against *P.aeruginosa*

- Ceftriaxone: Salmonlosis & gonorrhea
- Ceftriaxone & cefotaxime: PRSP,*S.pyogens* ,*N.meningitis*
- Anti-pseudomonas:

  Ceftazidime & Cefoperazone:

  可穿透至腦脊髓液中but Cefoperazone Poor penetration to BBB

3rd generation Cephalosporins

Flomoxef:由moxalactam 演化而來， MTT site chain---HTT site chain

G(+): 抗*Sta.aureus*,Streptococcus效力強

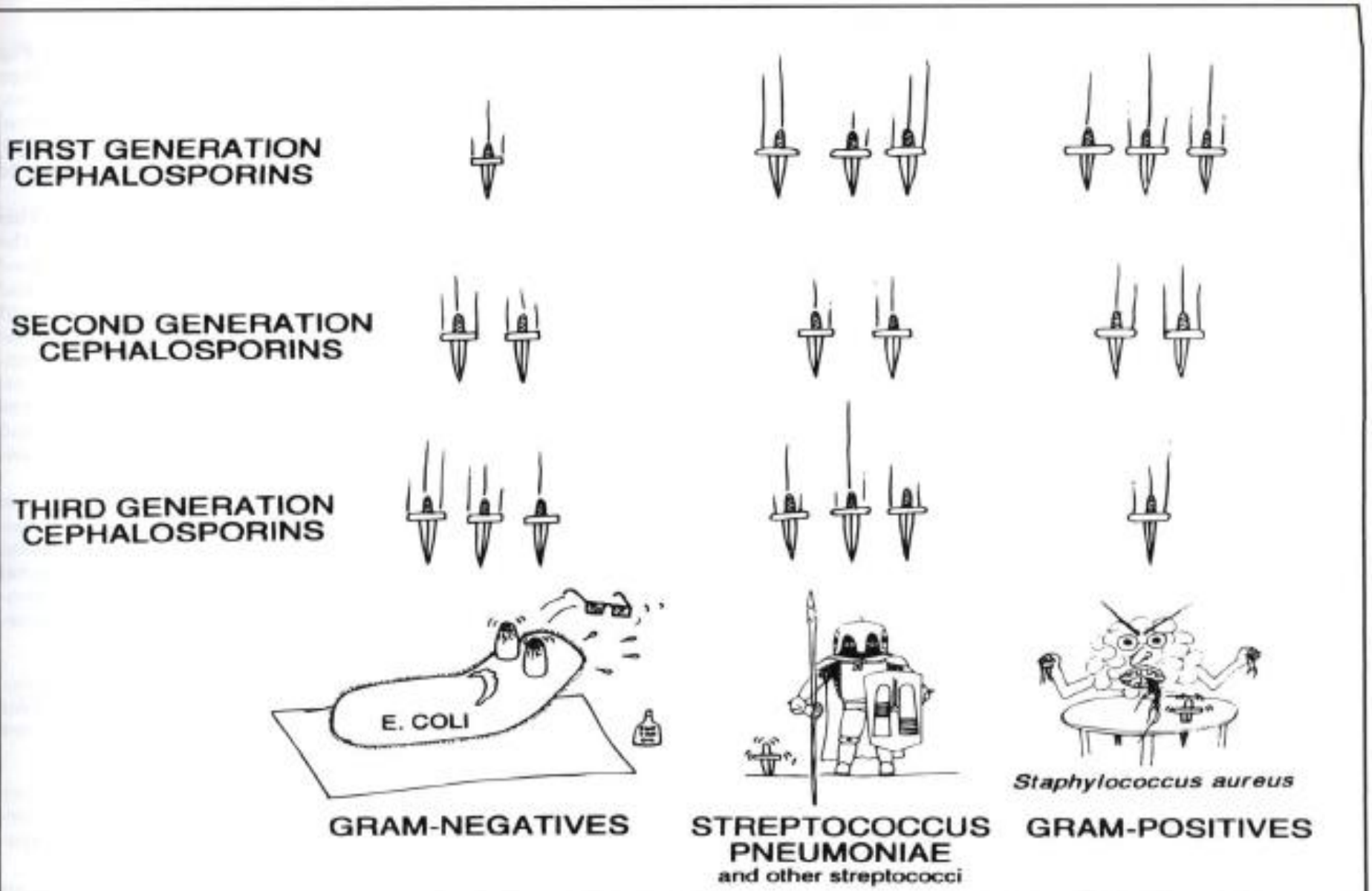
Streptococcus pneumoniae 無效

effective for anaerobes (*Bacteroides.fragilis*):治療輕至中度產生ESBL細菌感染

- More resistant enterobactereacea, such as *Enterobacter, Citrobacter, Serratia, Morganella* (若為有效，應combine aminoglycosides)

治療IAI, community acquired APN

Cephalosporins(2/7)



Cefxime(cefixmycin)

- PECK+HMN
- *Sta. aureus* 無效
- *Streptococcus pneumoniae*無效
- 400mg po qd or 200mg po q12h
- Maximum dose:400mg po q12h
- Urethra or throat Gonorrhea:400mg single dose

4th generation Cephalosporins

- Extended gram (+)(-) coverage
- Cefepime (1g–2 g IV q8–12h)
- Cefpirome (1-2 g IV)
- Cefepime v.s Cefpirome

  Pseudomonas aeruginosa

  對厭氧菌效果差, 可穿透至腦脊髓液中

5th generation Cephalosporins

ceftaroline

- Anti-ORSA Cephalosporin
- Anti-PRSP
- 對GPC 抗菌力較強
- 與ceftriaxone相似，對 Pseudomonas 無效
- 對Amp C 、ESBL無效
- Iv drip 1 hour
- 600mg iv q12h to q8h
- Pneumonia, ORSA bacteremia, endocarditis, osteomyelitis
- =vancomycin + ceftriaxone
- adjust dose in AKI

ceftobiprole

- Anti-ORSA Cephalosporin
- Anti-PRSP
- 對GNB 抗菌力較強
- 與ceftazidime相似，對 Pseudomonas 有效
- 對Amp C 、ESBL無效
- Iv drip 2 hours
- 500mg iv q8h
- Susceptible to Pseudomonas aeruginosa=ceftaroline + amikin
- =vancomycin + ceftazidime
- Adjust dose in AKI

Cefoperazone-sulbactam

Antimicrobial spectrum of CPZ/SUL (Brosym)

Zefotam

	Antimicrobial spectrum	Summary of Spectrum
G(+)	Staphylococcus spp.	Most G(+),except MRSA, Enterococcus
G(-)	Including: E. coli Citrobacter spp. Klebsiella spp. Enterobacter spp. Serratia, Proteus spp. P. aeruginosa H. Influenzae Acinetobacter spp.	All important G(-), including P. aeruginosa and A. baumannii (Except S. maltophila)
Anaerobes	Bacteroides	All important anaerobes (Except Clostridium species, but Clostridium perfringens is ok)

- Piperazine side chain againt(*P.aeruginosa*, Enterobacter) 具cefamandole 主結構和MTT side chain不易被 beta-lactamase 破壞
- Sulbactam can combinate with PBP2 active against *Acinetobacter baumannii (CRAB) Bacteroides fragilis*
- 膽道濃度高是血清的100倍
- 抗菌範圍: againt(*P.aeruginosa*, Enterobacter + AB, P.EC.K
- ORSA, Enterococcus,Stenotrophomonas 無效
- 中至重度的社區感染、混合型感染、院內感染，neutropenic fever
- 4gm iv q12h, high dose 4gm iv q8h for *P.aeruginosa* HAP,neutropenic fever, AB

Cefoperazone-sulbactam(brosym,zefotam)

SANFORD GUIDE 熱病

2020 THE SANFORD GUIDE

To Antimicrobial Therapy

Usual Adult Dosage

Cefoperazone-sulbactam 2-4 gm IV q12h

Adverse Reactions, Comments

In SE Asia & elsewhere, used to treat intra-abdominal, biliary, & gyn. infections.

Also used for a variety of respiratory, skin and urinary tract infections.

Other uses due to broad spectrum of activity.

10.器官可轉移性

腎和泌尿道	◎
肝臟，膽汁	◎
痰液，支氣管液	◎
骨髓	◎
盆腔	◎
臍帶血	○
骨	○
腹腔	◎
母親的乳汁	x
扁桃體	○
羊水	○
脊柱液	○
腸道	-
膿瘡	◎
肌肉和皮下組織	○
胸腔	◎
眼	-
肺泡	◎

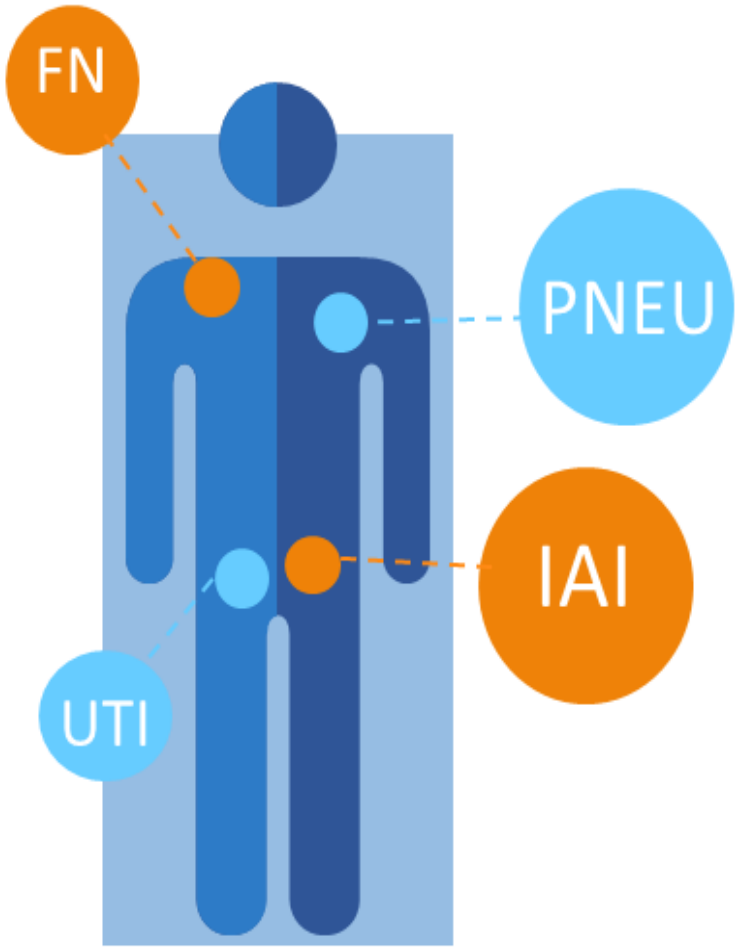
◎：≧25μg/ml
○：25>～≧6
△：6>～≧1
x：1>
-：データなし

2020 日本熱病

Approved indications and dosage

仿單適應症

- 上、下呼吸道感染
- 上、下泌尿道感染
- 腹膜炎、膽囊炎、膽管炎及其它腹腔內感染
- 骨盆發炎、子宮內膜炎及其它生殖道感染
- 創傷燙傷、手術後之二次感染



Suggested dosage

Adult : **4 g, q12h**

Pediatric : 160mg/kg/day,
divided into 2-4 times /day

Ceftazidime-avibactam(Zavicefta)

- Avibactam: beta-lactamase inhibitor---reversible combination to beta-lactamase
- Inhibit 1 beta-lactamase:1-5 avibactam
- Inhibit 1 beta-lactamase:10-100 other beta-lactamase inhibitor
- Can inhibit: narrow-spectrum beta-lactamase、ESBL、AmpC beta-lactamase、KPC
- Tx: IAI、UTI、nosocomial infection of CRE、G(+):Streptococcus, anaerobes: invalid
- Side effect: hepatitis, thrombocytopenia, skin rash

Ceftolozane-tazobactam

- Most effective antibiotic to *Pseudomonas aeruginosa*
- Not good for anaerobes
- G(+): Streptococcus
- Tx: IAI,UTI,nosocomial infection
- Side effect: nausea, vomiting, diarrhea

Carbapenem

- Imipenem/cilastatin (Tienam)（cilastatin為DHP-1抑制劑）

  Meropenem (Mepem)
- G(+),G(-),anaerobes: severe polymicrobial infections
- Not effective to *ORSA,ORSE,S. maltophilia, Burkholderia cepacia, vancomycin*-resistant *enterococci, Clostridium difficile*

Imipenem v.s meropenem

- Imipenem is more good effect to G(+) and *A.baumannii*
- Meropenem is more good effect to G(-)
- Imipenem can not penetrate BBB, but meropenem can penetrate
- Seizure side effect: imipenem > meropenem
- Cost: meropenem > imipenem

Aminoglycosides

- Synergy for Entercoccus, *Sta. aureus,*
  viridans streptococci
- Synergy for G(+): gentamicin best
  for G(-): amikacin best
- Potency: amikacin is the lowest, but lowest resistance

副作用:

- Neuromuscular blockade: myasthenia gravis, muscular dystrophy
- Nephrotoxic: gentamicin > amikacin>netilmycin
- Vestibular damage: gentamicin > amikacin
- Auditory disorder: Streptomycin > amikacin

無法穿透至腦脊髓液中、對厭氧菌，酸性環境完全無效

Once-daily aminoglycosides

Estimation of creatinine clearance (mL/min) from serum creatinine values

$$\frac{(140-\text{Age}) \times \text{B.W in Kg}}{72 \times \text{Cr in mg/dL}}$$

Female= above value x 0.85

- A significant PAE for aerobic GNB (2-8H)

  Dependent on neutrophil function
- Concentration-dependent
- Adaptive post-exposure resistance
  - More frequent dosing of aminoglycosides tends to reduce their uptake into the bacterial cell of aerobic GNB
- Advantage: more effective, safe, convenient

Infect Dis Clin N Am 2003;17:503-28

Aminoglycosides

- Dosage: based on IBW (idea body weight)
- 不能使用once daily dosing 的場合：

– Impaired renal function

(ex. CCr < 60, hemodialysis, peritoneal dialysis)

–Altered volume of distribution

(ex. ascites, severe burn)

–Neutropenia

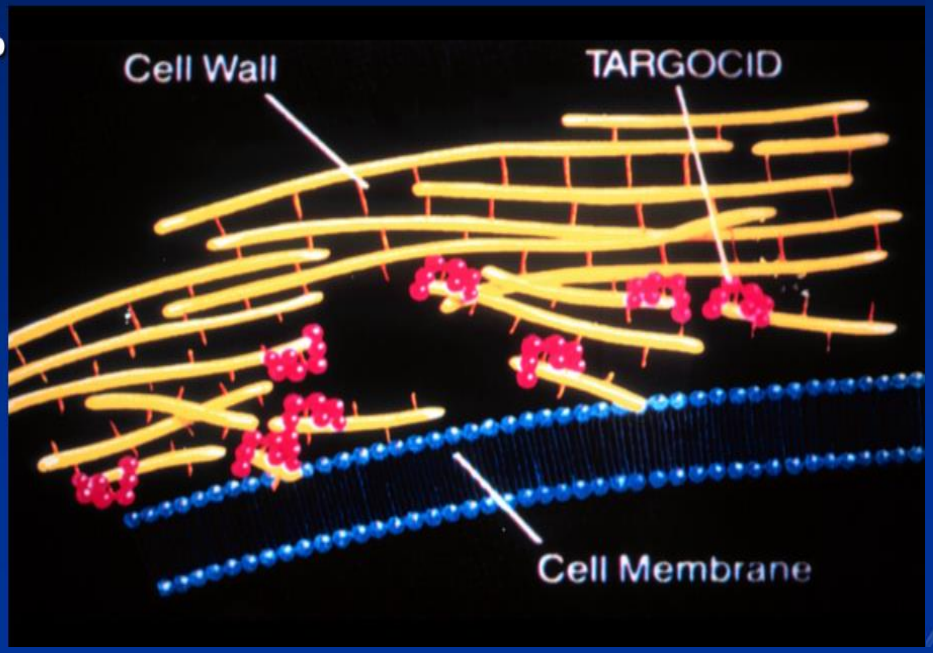
–Combination with beta-lactam for GPC infection

Aminoglycosides

- 目前使用的狀況：
- –因為擔心aminoglycosides的腎毒性，目前臨床的使用量逐年下降
- 許多抗藥性細菌對aminoglycosides的感受性增加
- –多半和beta-lactams一起使用，著眼於synergistism的效果
- –使用於治療*non-tuberculous mycobacterium*
- Imipenem, aminoglycosides, macrolides

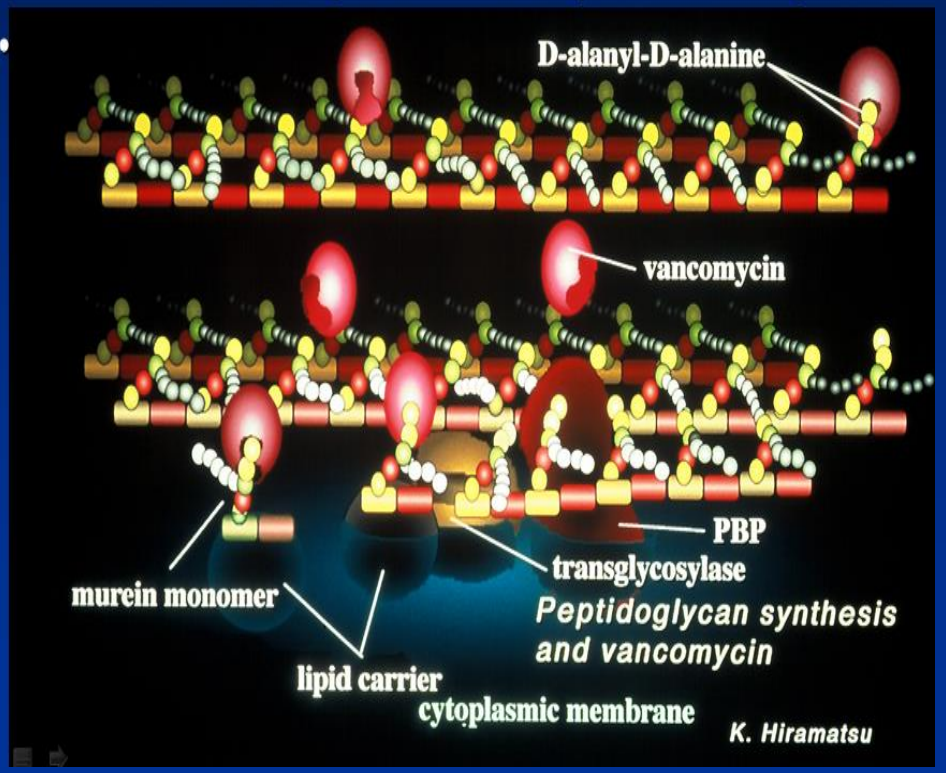
Glycopeptides

- teicoplanin 與peptidoglycan結合 to inhibit cell wall synthesis – cell lysis
- Vancomycin
- Bacteriocidal except enterococci (bacteriostatic)



Vancomycin

- 與細胞壁胜醣peptigoglycan前質結合抑制細胞壁合成
- Bacteriocidal except enterococci (bacteriostatic)



Glycopeptide

- Vancomycin
- IV
- Red man syndrome
- Oral form: *C. difficile* colitis
- Poor cross BBB
- Resistant pneumococcal meningitis
- Ototoxicity,renal toxicity
- Drug fever

- Teicoplanin
- IV/IM
- Much less side effects
- No oral form
- Poor cross BBB

Glycopeptides

- Adverse effect
- Red man or neck syndrome: histamine release, Infusion-related toxicity
- –需要較多的稀釋液 fluid overload
  - Skin itching, flushing, angioedema, hypotension
- GI disturbances
- Headache and rash
- 可逆性白血球、血小板減少
- Thrombocytopenia 2.4%
- –Delayed skin rash, marrow suppression
- Ototoxicity, nephrotoxicity – with aminoglycosides

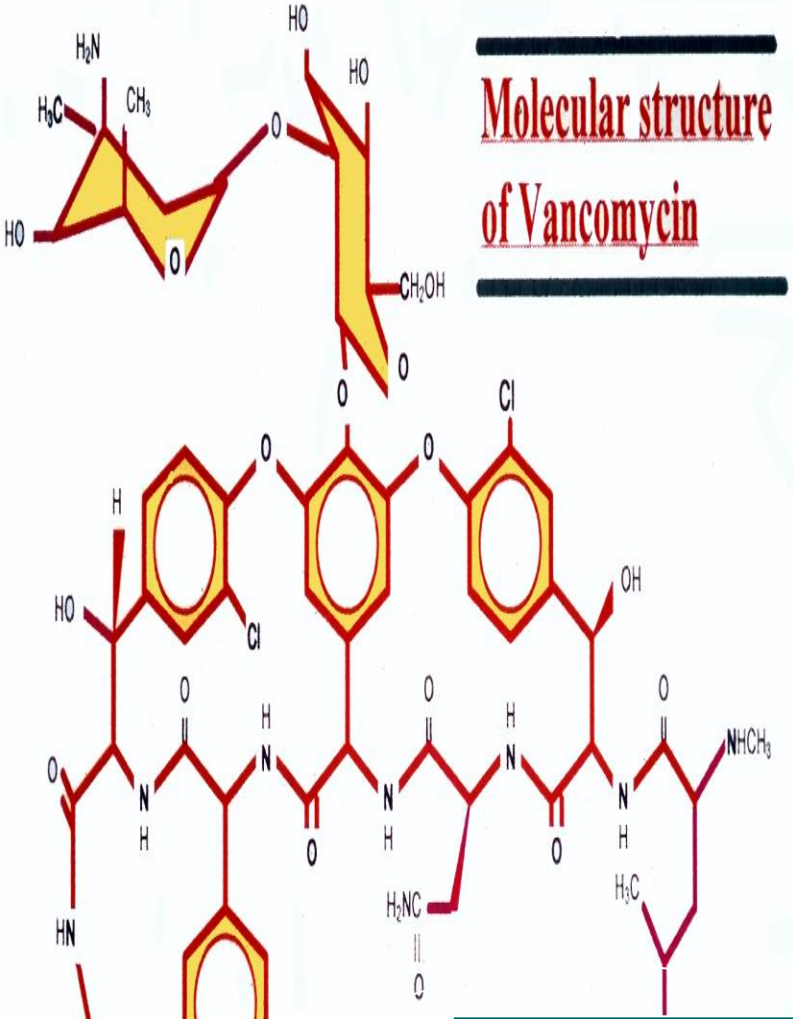
Spectrum of Glycopeptides

- Susceptible to Gram-positive bacteria
- –Teicoplanin is more potent against *Streptococcus* spp.
- –Teicoplanin is more potent against *Enterococcus* spp.
- •Esp. for VanB phenotype VRE
- –Teicoplanin has slower bactericidal activity against Gram-positive pathogens than vancomycin
- –Teicoplanin is less potent against coagulase negative Staphylococci, esp. *S. epidermidis*, *S. haemolyticus, S. hominis, S. warneri,* and *S. xylosus.*

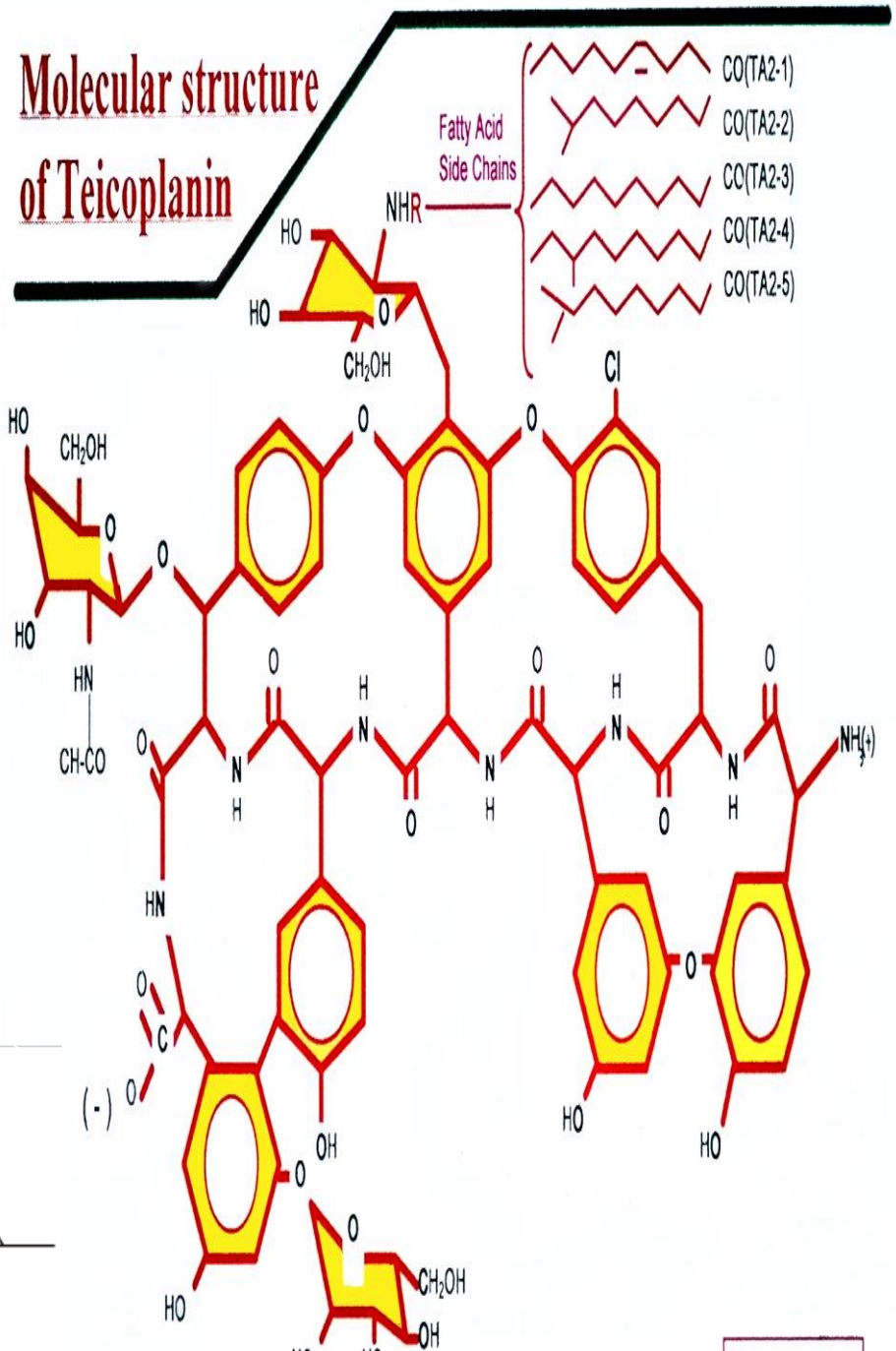
Dosage of Glycopeptides

- Both time- / AUC dependent antibiotics
- –Trough levels:
- 10 mg/L for vancomcyin
- 10 mg/L ~ 20 mg/L (endocarditis) for teicoplanin
- Loading dose:
- –Vancomycin: 25 mg/Kg
- –Teicoplanin: 6 ~ 12 mg/Kg q12h for 3 doses, qd for 1 dose
- Maintenance dose:
- –Vancomycin: 15 mg/kg q12h (may up to 4 g/d)
- –Teicoplanin: 6 ~ 12 mg/Kg (even up to 30 mg/kg) qd

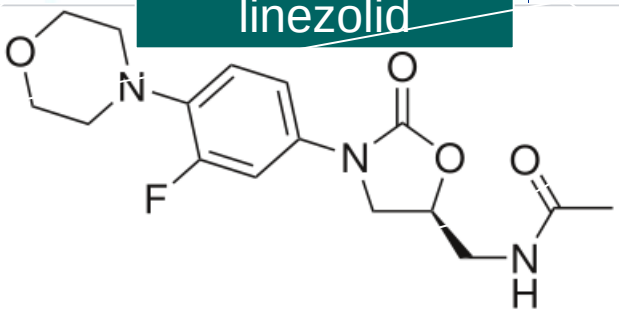
Molecular structure of Vancomycin



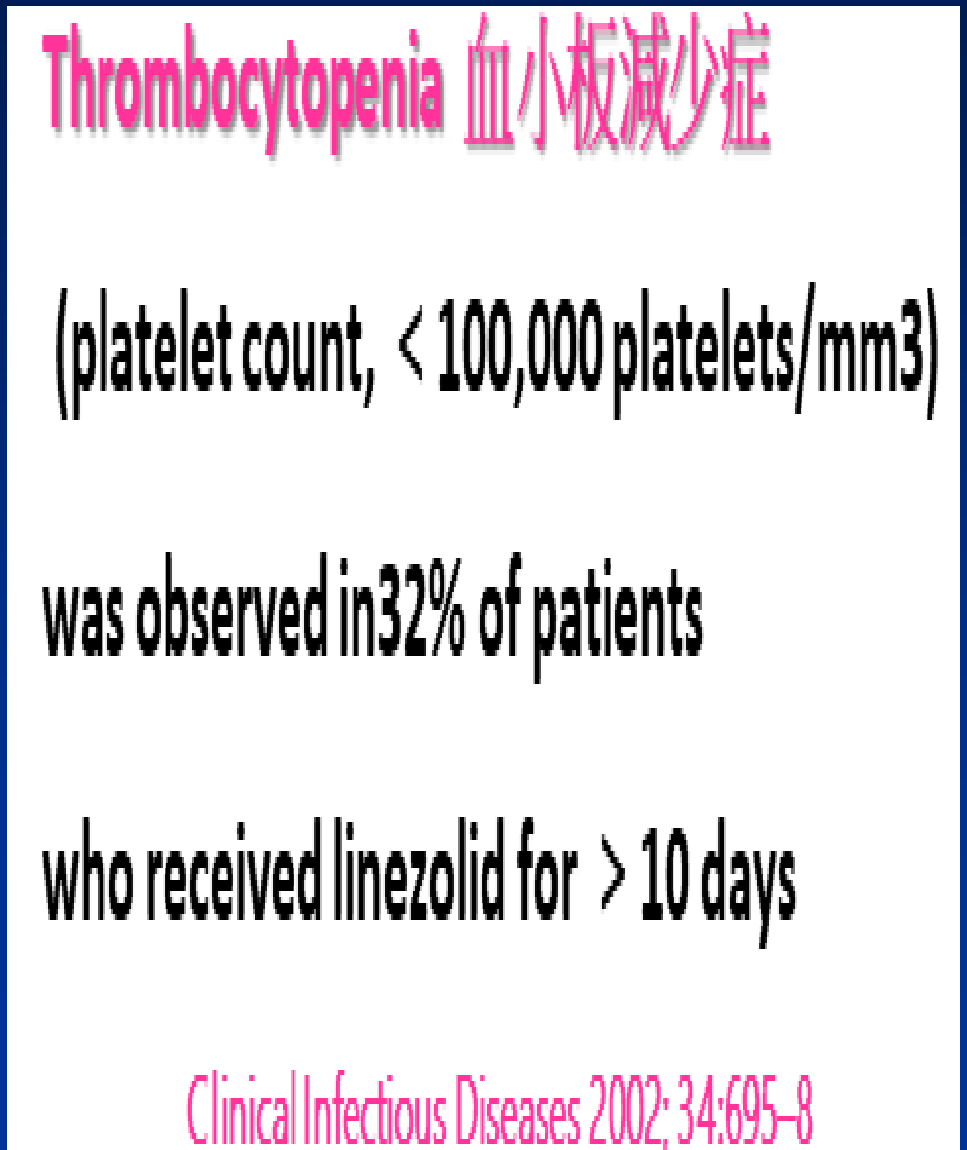
Molecular structure of Teicoplanin



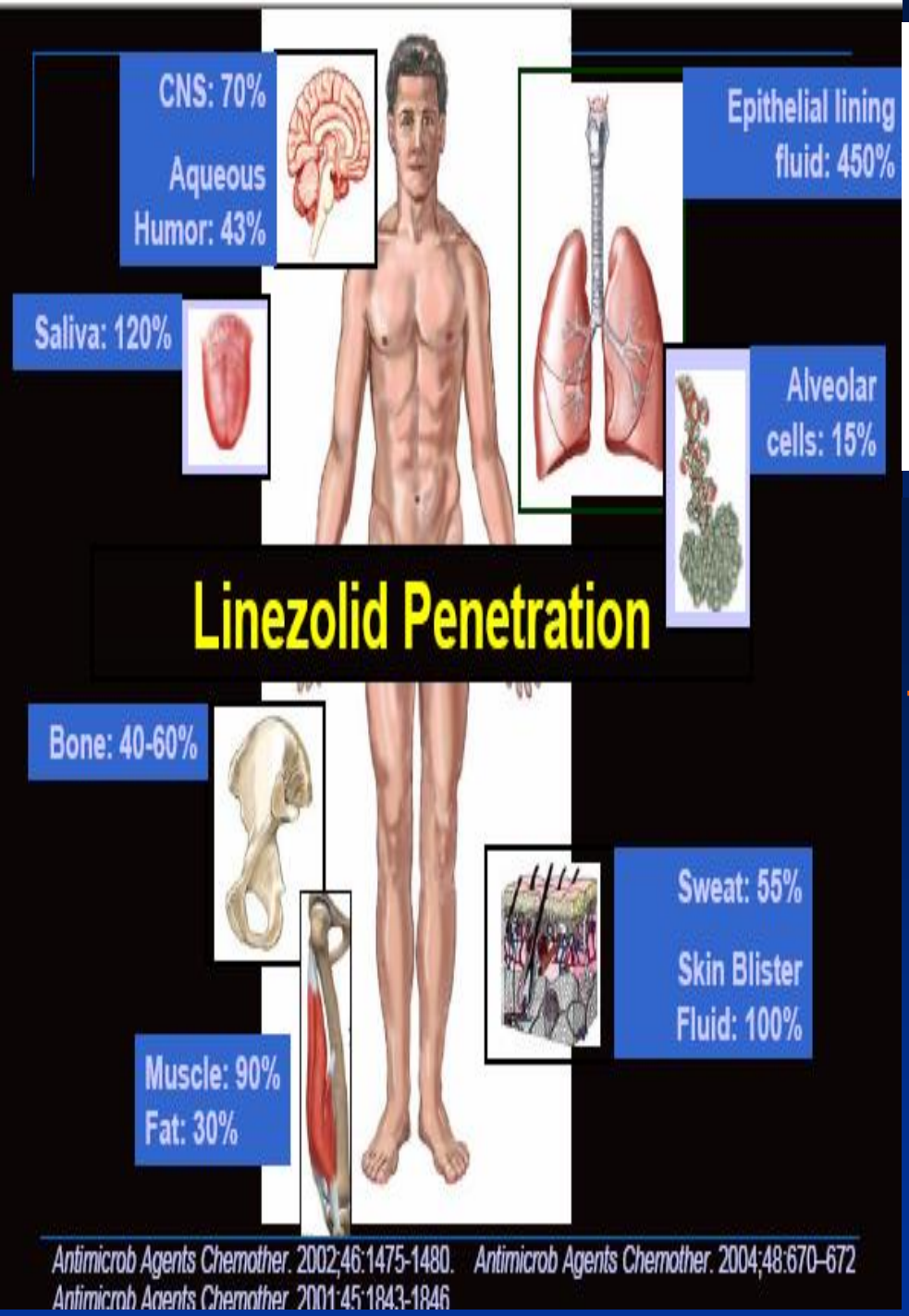
linezolid



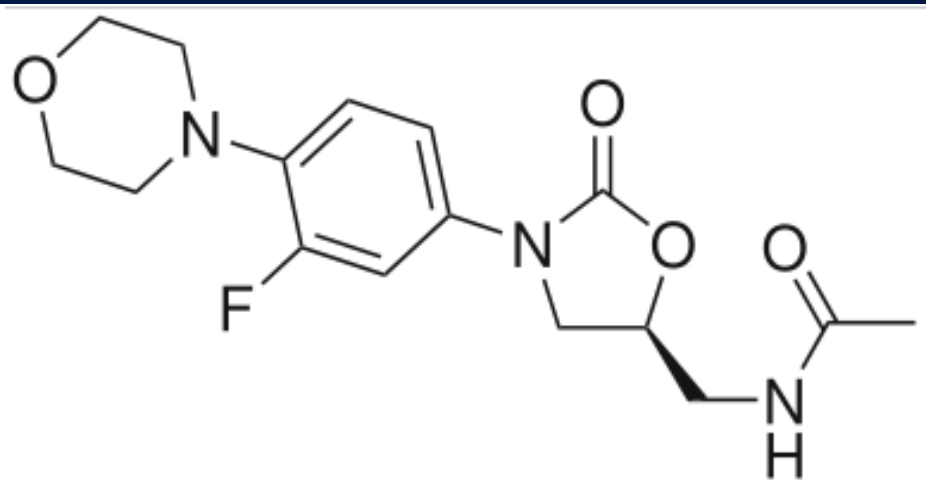
Oxazolidinones (linezolid:Zyvox)



- Oral, completely absorbed in GI tract
- Inhibit RNA translation by binding to 30S ribosomal RNA of the 50S subunit to prevent the formation of a functional 70S initiation complex
- ORSA,VRE,GISA
- Diarrhea, nausea, headache,Abnormal liver function



Antimicrob Agents Chemother. 2002;46:1475-1480. Antimicrob Agents Chemother. 2004;48:670–672
Antimicrob Agents Chemother. 2001;45:1843-1846

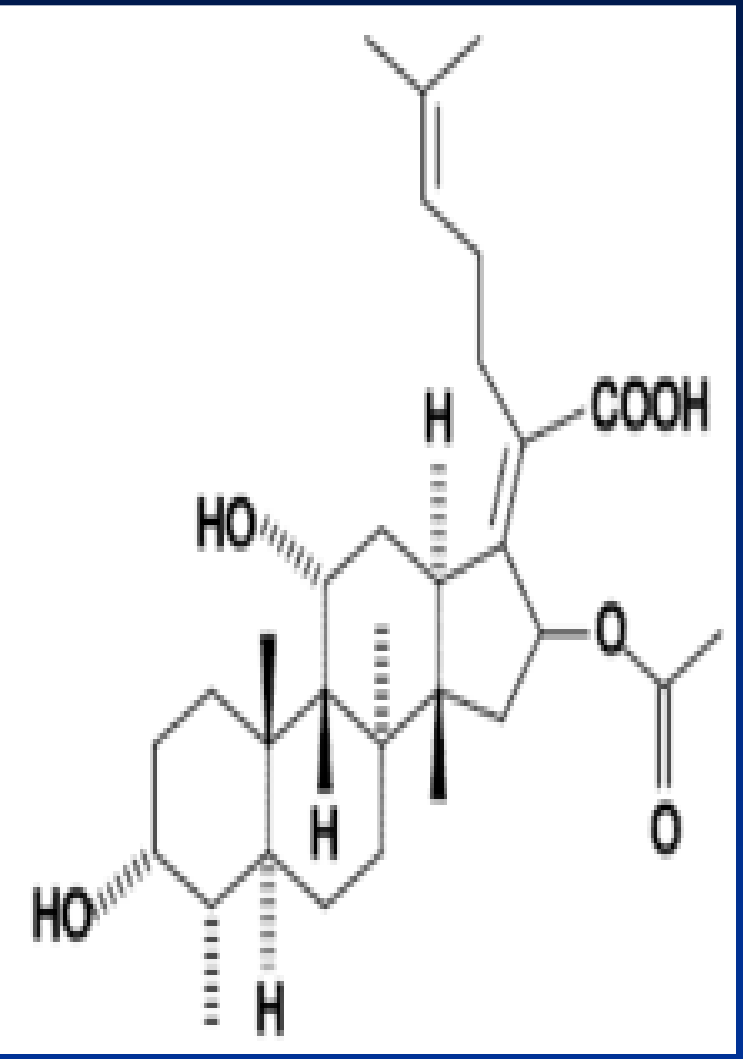


Drug Penetration Issues: % tissue/serum

Tissue	Vancomycin	Teicoplanin	Linezolid
Bone	7%–13%[1]	~50%–60%[8]	60%[12]
CSF	0%–18%[2,3]	~10%[9]	70%[13]
ELF	11%–17%[4,5]		450%[13]
Inflammatory blister fluid		77%[10]	104%[14]
Muscle	~30%[6]	~40%[11]	94%[12]
Peritoneal dialysis fluid	~20%[7]	~40%[10]	61%[15]

1. Graziani 1988; 2. Matzke 1986; 3. Albanese 2000; 4. Georges 1997; 5. Lamer 1993; 6. Daschner 1987; 7. Blevins 1984; 8. Wilson 2000; 9. Stahl 1987; 10. Wise 1986; 11. Frank 1997; 12. Lovering 2002; 13. SmPC; 14. Gee 2001; 15. Gendjar 2001.

Fucidic acid



- Steroidal abx inhibit protein synthesis(50S)
- Hepatic metabolism, biliary excretion
- Tissue penetration:

  skin blister: 46-75%

  sputum: 6-8%

  CSF: 0.3%

  Brain: 2.5%

  burn crusts: 171-642%

  synovial fluid: 68-78%

  infected bone: 16-30%
- bioavailability

Capsular formation: 69%

Suspension: 46%

Film-coated tablet: 91%

Fluoroquinolone

作用於Topoisomerase 4 異構酶抑制DNA 複製
作用於DNA gyrase 促旋酶

- 1st: cinoxacin: GNB
- 2nd:fluoroquinolones

  Ciprofloxacin(oral bioavailability70%)

  ofloxacin(100%), pefloxacin:

  GNB,GPC *(S.aureus*),atypical (Mycoplasma, Legionella,Rickettsiae,Mycobateria)
- 3rd:levofloxacin (PRSP)
- 4th:moxifloxacin,gemifloxacin,gatifloxacin:GNB,PRSP,atypical,anaerobes – not for nosocomial infection

Properties of newer quinolones

- Broad spectrum activity
  - Gram-negative bacteria
  - Improved against Gram-positive bacteria
  - Improved against anaerobes
- Once daily dosing (dose-dependent)
- Some with apparent reduced risk of selection of resistance

2nd,3rd,4th Fluoroquinolones Spectrum of activity

- *Enterobacteriaceae*
- *Haemophilus* spp. *Neisseria* spp.
- *Legionella*, *Mycoplasma*, *Chlamydia*
- *Pseudomona aeruginosa*
- Staphylocci (MSSA, MSSE)
- Streptococci (+/- enterococci)
- Anaerobes
- Mycobacteria (*M. tuberculosis, M. kansasii, M. fortuitum*)

Levofloxacin

- **Active to *S. pneumoniae* (including PRSP)**
- **Active to *Pseudomonas aeruginosa***
- **Active to atypicals**
- Higher penetration to lung tissue for levofloxacin
- **Bactericidal: penetrate respiratory tissues in excess of MICs**
- **Treat sinusitis, bronchitis, community-acquired pneumonia and UTI, chlamydial urethritis**

Moxifloxacin

- **Active to *S. pneumoniae* (including PRSP)**
- **Active to atypicals**
- **Active to anaerobes (aspiration (10%))**
- **Monotherapy of intra-abdominal or skin and soft tissue infections, because of its antianaerobic activity, resistance among *B.fragilis* is increasing**

Indication of Fluoroquinolone(1/4)

- Primary indication:
- –Community-acquired infection:
- •sinusitis
- •Lower respiratory tract infection:(newer FQs only)
- –Pneumonia: Both typical and atypical
- –Acute exacerbation of COPD
- •Salmonellosis
- –Complicated UTI
- –Intra-abdominal infection
- –Soft tissue infection

Indication of Fluoroquinolone(2/4)

- Primary indication:
- –Nosocomial Infection: Ciprofloxacin & levofloxacin
- *Pseudomonas aeruginosa*: VAP, HAP
- ESBL producing strain
- *Stenotrophomonas maltophilia*: levofloxacin, moxifloxacin
- Legionellosis
- Other β-lactams resistant pathogens

Indication of Fluoroquinolone(3/4)

- Primary indication (continued)
- –Mycobacterial infection
- •*M. tuberculosis* and NTM
  :levofloxacin,moxifloxacin
- –Site specific infection:
- •Chronic prostatitis
- •Chronic epididymitis

Indication of Fluoroquinolone(4/4)

- Secondary indication:
- –Allergy to β-lactams
- Immediate type
- Delayed type
- –IV – Oral switch

Adverse Drug Reactions of FQs

- Well-tolerated, generally < 3%
- •Nausea, diarrhea, dizziness, headache, abdominal pain, vomiting, dyspepsia, abnormal liver functions, taste perversion, skin rashes …etc.
- •Cardiac arrythmia (torsades de pointes)-1/106
- •CNS toxicity (1-4%) and seizure (rare)
- •Bone marrow suppression (1-2%)
- •Very rare- phototoxicity, anaphylaxis, tendon rupture..

Drug-Drug Interactions for FQs

- Antiacids containing aluminum and magnesium salts.
- Iron or zinc preparations.
- Sucralfate, cimetidine, ranitidine, warfarin, cyclosporin, rifampin, oral contraceptive steroids, benzodiazepine, nonsteroidal anti-inflammatory drugs, metronidazole, theophylline, caffeine
- Avoid simultaneously with antacids, vitamines, dairy products, citrate, foods

Sulfamethoxazole/Trimethoprim (TMP/STX)

- Baktar (oral), Sevatrim (IV),bactericidal
- 臨床用於：
- –UTI (especially cystitis)
- –Traveler's diarrhea / Salmonellosis
- –*Stenotrophomonas maltophilia* infections
- –*Pneumocystis jerovecii* pneumonia (PJP)
- –Toxoplasmosis
- –Nocardiosis

Clindamycin

- G(+), anaerobe, *Toxoplasma gondii, P. carinii*
- Mechanism of action:抑制細菌蛋白質之合成, 抑菌作用 (bacteriostatic),Bone:bactericidal
- Reduce toxin-production of *S. aureus, S. pyogens*
- Intraabdominal, pelvic infection, DM foot

  Necrotizing pneumonia, lung abscess, empyema, aspiration pneumonia, recurrent tonsillitis,STSS
- GI- 10% Nausea, vomiting, diarrhea, *C. difficile* colitis (pseudomembrane colitis)
- 10% morbilliform rash
- Poor into CNS
- Community acquired-MRSA

Clindamycin

- Spectrum:
- –GPC (resistance rate 20~70%)
- –Anaerobes (resistance rate ~50%)
- •角色：
- –治療 GPC 的替代藥物 (beta-lactam allergy)
- 確定”S” to Clindamycin
- –Group A *streptococcus* necrotizing fasciitis
- –*Staphylococcal* or *Streptococcal* toxic shock syndrome
- Combination with beta-lactams

Metronidazole

- Anaerobe, antiprotozoal effects阿米巴原蟲, 陰道滴蟲
- Bacteriocidal
- excellent tissue penetration - Abscess formation, polymicrobial infections, bacterial vaginitis, *C. difficile* colitis, brain abscess (well into CNS), *C. perfingens*
- GI- unpleasant metallic taste, nausea, vomiting

  Peripheral neuropathy

  Rare- seizure, encephalopathy, cerebellar dysfunction

  Alcohol – disulfiram-like reaction
- Interaction with warfarin

Tigecycline 的藥物動力學特性

- 血清濃度-低：不能治療 bacteremia: 組織濃度-高：能夠治療 tissue infections
- Indication: IAI, skin & soft tissue infection
- Lung and kidney: low concentration

Tigecycline 的殺菌範圍

- 殺菌效力：包括下列細菌
  1. G (+) cocci (包括抗藥性細菌)
  2. G (-) bacilli (包括抗藥性細菌)
  3. Anaerobes (包括 Bacteroides fragilis)
  4. Atypical pathogens
- 下列 G (-) bacilli，tigecycline 缺乏殺菌效力
  1. Pseudomonas aeruginosa
  2. Proteus mirabilis
  3. Proteus valgaris
  4. Providencia spp
  5. Morganella morganii
  6. Burkholderia cepacia

Tigecycline 不能做為經驗性抗生素使用

- Tigecycline 的血清濃度太低,脂溶性抗生素，對組織穿透性好
  1. 嚴重感染症可能併發 bacteremia
  2. Tigecycline 不能治療 bacteremia
- Tigecyline 對 *P. aeruginosa*、*P. mirabilis* 無效
  1. 會考慮使用 tigecycline 的感染症通常是嚴重的感染症（如 nosocomial infection)
  2. 治療嚴重的感染症的經驗性抗生素選擇：必須考慮 *P. aeruginosa* 為可能的致病菌
- 副作用:胰臟炎
- Diarrhea: 13%
- GOT, GPT, ALP, PT, PTT
- •Skin reactions: urticaria, maculopapular rash, pruritus

Anti-*P. aeruginosa*

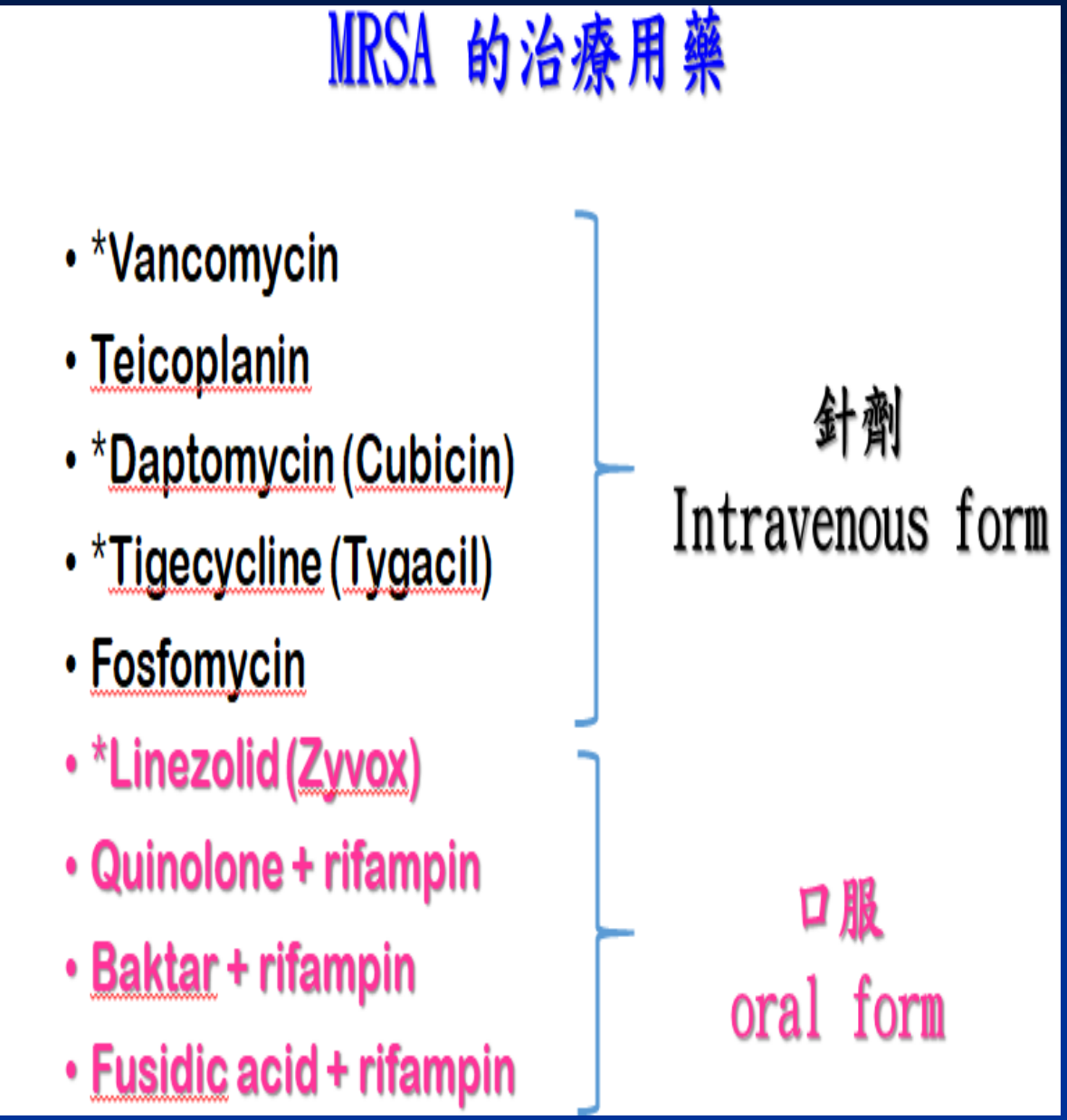
- Ceftazidime,Cefoperazole Cefepime,
- Ciprofloxacin, Levofloxacin

  Piperacillin, Piperacillin/Tazobactam

  Ceftolozane/tazobactam

  Ceftazidime/avibactam
- Carbapenem
- Aminoglycosides

MRSA antibiotics treatment



- Glycopeptide
  Vancomycin
  Teicoplanin
- Linezolid (Zyvox)
- Rifampin
- Minocycline
- Baktar
- Fucidic acid
- Tigecycline
- Daptomycin
- Moxifloxacin
- Clindamycin
- Ceftaroline
- Cefobiprole
- Nemonoxacin

MRSA antibiotics treatment

臨床感染症	首選藥物	替代藥物
菌血症（含感染性心內膜炎）	Vancomycin 15mg/kg q12h Daptomycin 6 – 10 mg/kg.day	Quinupristin/dalfopristin, TMP-SMX, linezolid, telavancin
肺炎	Vancomycin 15 mg/kg.q12h Linezolid 600 mg q12h	Clindamycin, respiratory fluoroquinolones, TMP-SMX
皮膚與軟組織感染	門診病患：clindamycin, TMP-SMX, doxycycline, linezolid 住院病患：vancomycin, linezolid, daptomycin, telavancin, clindamycin	
骨關節感染	Vancomycin, daptomycin, TMP-SMX, linezolid, clindamycin	
中樞神經感染	Vancomycin (not teicoplanin) ± rifampin	Linezolid, TMP-SMX

Colistin

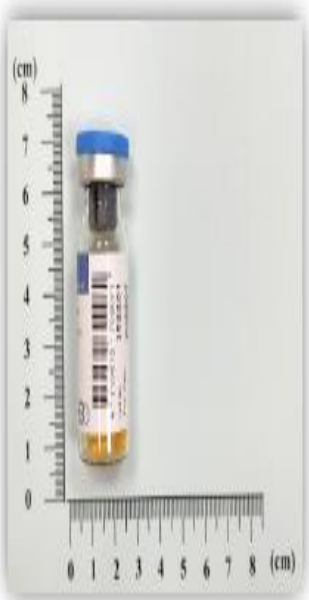
- Developed in 1947
- –Available for clinical use in the 1960s
- –Not used due to nephro- and neurotoxicity in 1970s
- •Emerging of MDR pathogens (esp. *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae*)
- –Use Colistin again for MDR GNB

Colistin

- 2.5-5mg/kg iv divided q12h are bactericidal polypeptide kill GNB by disrupting the cell membrane
- Inactive against *Proteus, Providencia and Serratia*
- Inhaled colistin 75-150mg q12h given by nebulizer
- Significant nephrotoxicity up to 20%,
- Paresthesias, slurred speech, peripheral numbness, tingling

Minocycline

英文品名	Menocik Lyophilized Injection 100mg "Biogend"		
適應症	革蘭氏陽性、陰性菌、立克次氏體及巨型濾過性病毒等引起之感染症。		
劑型	243凍晶注射劑	包裝	10毫升Type I玻璃小瓶裝 10支盒裝
標籤、仿單及包裝加註			
藥品類別	05限由醫師使用	管制藥品分類級別	
藥品分類	一般學名藥	監視對象	
主成分略述	MINOCYCLINE HCL		



In US, minocycline was introduced in the 1970s; IV formulation was withdrawn in 2005 but was back in 2009 for MDR pathogens.

Minocycline-based regimen for nosocomial MDRAB infections

- Systematic review. 10 (9 retrospective case series and 1 prospective single center trial) out of 2990 articles.
- 218 patients received minocycline. Monotherapy (18, 8.3%) vs combination (200, 91.7%; most ***cefoperazone/sulbactam***, ***colistin***, or ***carbapenems***).
- 100 mg q12h with or without a loading dose of 200 mg (8 studies); 200mg bid (1) and 200mg qid (1).
- Majority were pneumonia (80.6% with 50.4% ventilator-associated pneumonia).
- The clinical and microbiological success rates were 72.6% and 60.2%, respectively.

CRAB & Elizabethkingia

IDSA guidance for CRAB

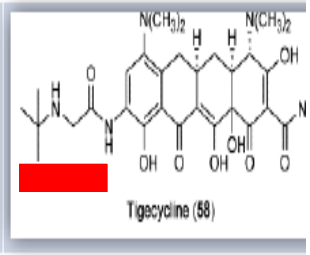
- Mild infections:
  - ampicillin-sulbactam (preferred, 18g/d),
  - alternative: minocycline, tigecycline, polymyxin B (colistin for cystitis), or cefiderocol
- Mod to severe infection: Combination therapy with at least two in vitro active agents
  - ampicillin-sulbactam (preferred, 24g/d), minocycline (200mg q12h), tigecycline (100mg q12h), polymyxin B, extended-infusion meropenem, or cefiderocol
  - (not meropenem plus colistin)

伊莉莎白菌 (*Elizabethkingia* spp.)

- 廣泛存在於院內的環境，隨著被伊莉莎白菌感染個案報導的增加，再加上伊莉莎白菌本身的多重抗藥性及被伊莉莎白菌感染後病患的高死亡率，相關的伊莉莎白菌感染與院內感染已成為越來越重要的議題
- 感染伊莉莎白菌的病患之間享有一些共通的危險因素 (risk factors)，包括感染多發生在長時間住院、曾使用廣效抗生素、加護病房患者、使用呼吸器、免疫力較差、或有多重共病症的患者

Minocycline & Tigecycline

Minocycline vs. Tigecycline

	Minocycline	Tigecycline
Structure 側鍊與分布有關		
Indication	Wide range of infections caused by several GNB	Skin and soft tissue infections, complicated intra-abdominal infection
Resistant mechanism		
Usual dose	200 mg PO/IV loading, then 100 mg PO BD	100 mg IV loading, then 5 mg IV BD
Volume of distribution (L)	80–115	350–500
Cmax (mg/l)	4.2 (200 mg IV dose)	0.82 (100 mg dose)
AUC 24 mg/[hr·L]	45	2.2 +/- 0.3 mg

Summary

- Routine testing of minocycline for *Acinetobacter* spp., *S. maltophilia*, *B. cepacia* complex is recommended by CLSI.
- Minocycline showed high susceptibility; recommended as one of the combination antibiotics for severe CRAb infection.
- Minocycline consistently shows in vitro activity against *Elizabethkingia* spp.

Minocycline注射劑新版健保給付規定

第10節 抗微生物劑 Antimicrobial agents

（自114年1月1日生效）

10.8.9.Minocycline注射劑：

限經感染症專科醫師會診，且符合下列條件之一使用：

1. 對Carbapenem具抗藥性之Acinetobacter baumannii感染(CRAB)。
2. CRAB以外具敏感性之抗藥性菌株。(114/1/1)
3. 其他臨床上懷疑或確定由立克次氏體、披衣菌等引起之感染。(114/1/1)

Minocycline 是治療*M. pneumoniae*首選

Mycoplasma pneumoniae	Doxycycline 100 mg IV/PO bid x 7–14 days Minocycline 200 mg PO/IV x 1 dose, then 100 mg PO/IV bid x 7–14 days	Azithromycin 500 mg PO on day 1, then 250 mg PO qd x 4 days Levofloxacin 750 mg PO/IV qd × 7–14 days Moxifloxacin 400 mg PO/IV qd × 7–14 days	Depends on regimen
Chlamydophila pneumoniae	Azithromycin 500 mg PO on day 1, then 250 mg PO qd x 4 days	Clarithromycin 500 mg PO q12 h × 10 days Doxycycline 100 mg IV/PO q12 h × 10 days Levofloxacin 500–750 mg PO/IV qd × 7–10 days Moxifloxacin 400 mg PO/IV qd × 10 days	Depends on regimen
Legionella species	Levofloxacin 750 mg IV/PO qd Moxifloxacin 400 mg IV/PO qd Azithromycin 1000 mg IV day 1, then 500 mg IV/PO qd Clarithromycin 500 mg PO q12 h	Doxycycline 100 mg IV/PO q12 h	7–10 days

Clinicians should practice prudent use of macrolide drugs due to the emergence of macrolide-resistant strains of *M. pneumoniae* (CDC, 2022).

Minocycline v.s Doxycycline

- IV drip over 1 hour
- Loading dose:200 mg IV/PO
- Maintain dose:100mg IV/PO q12h
- Side effect:
  vestibular:female:70%,male:23%

  Dizziness,
  vertigo,
  tinnitus ,
  nausea,
  vomiting

- For *Mycoplasma pneumoniae* infection empirical therapy due to resistent to macrolides 23% in Taiwan(2013)
- GI tract excretion
- photosensitivity

- Treatment VRE

- Linezolid
- Tigecycline (ORSA,VRE,PRSP,CRAB,CRE,ESBL, Amp-C), Pseudomembranous colitis

- Treatment CRAB

- 1.Minocycline
- 2.colimycin
- 3.tigecycline
- Tx:CRPA–Colistin
- Tx:CRE:–Tigecycline, colistin

Clostridium difficile

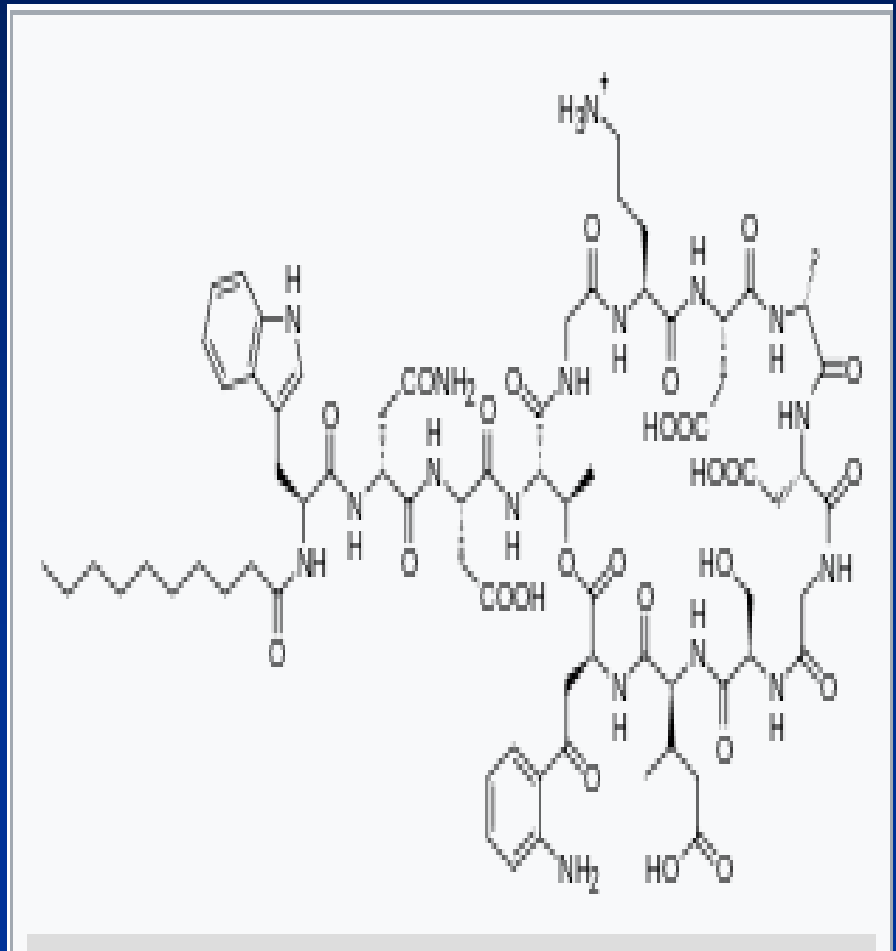
- Fidaxomicin
- 200mg po q12h x10 days
- Less selection to VRE

- Vancomycin 125mg po qid x 10 days
- Metronidazole 500mg tid x 10 days
- 均可induce VRE

Daptomycin(cubicin)

- bacteriocidal effect for MRSA;Enterococcus;Streptococcus
- Not treat for pneumonia due to large molecular & inactivated by surfactant
- 4mg/kg IV q24h SSTI
- 6-10mg/kg q24h for BSI
- AUC/MIC dependent antibiotics
- –May up to 10 – 12 mg/kg.day
- for infective endocaritis, bacteremia,osteomyelitis ,SSTI

  Not indicated for pediatric group,



Echinocandins(1)

- Caspofungin acetate(cancidas) 70mg IV loading dose, followed by 50mg IV q24h;
- against Aspergillus and azole-resistent Candida, 對*C.parapsilosis* MIC較高,
- not againt Cryptococcus, Mucor, Histoplasmosis,Blastomycosis and Coccidioides
- Neutropenic fever
- *Pneumocystis jirovecii* Pneumonia最後一線用藥
- Side effect: fever, nausea, phlebitis
- 肝腎功能不好要減量

Echinocandins(2)

- Micafungin sodium 100mg IV q12h for candidemia, 150mg IV for esophageal candidiasis
- Side effect: elevated LFTs and rare case of rash and delirium
- 肝腎功能不好不必減量

Echinocandins(3)

- anidulafungin (eraxis)200mg IV loading dose, followed by 100mg IV q24h, no dose change necessary in renal or hepatic insufficiency
- Side effect: elevated LFTs and hypokalemia and histamine-mediated reactions
- 肝腎功能不好不必減量

Voriconazole

- 對Aspergillus抗菌效力比amphotericin B，itraconazole強
- *Candida glabrata*，*Candida krusei*有效
- Cryptococcus neoformans，Fusarium，Dermatophytes
- Tx: Aspergillus ，systemic candidal infection 引起的 neutropenic fever
- 可治fungal meningitis(30-68% of serum)
- 不可治 Candidal UTI
- Side effect:

  visual disturbance 20.6% ,usually < 30min ,

  need to DC drug < 1%

  sun sensitivity:6%，hepatitis:13%，QTc interval prolong

Treat mold

- **Posaconazole**
- Tx:Mucormycosis, Fusarium,Candida, Aspergilus
- 與高脂食物併用可增加吸收3.9倍

- **Itraconazole**
- Tx:Dermatophytes,Aspergilus, Candida, Cryptococcus neoformans
- 與酸性食物併用可增加吸收45% ⟶55%
- Onychomycosis:

  200mg po qd x 6wks fingernail

  200mg po qd x 12 wks toenail

  Child C, CHF 禁用


Thanks for your attention