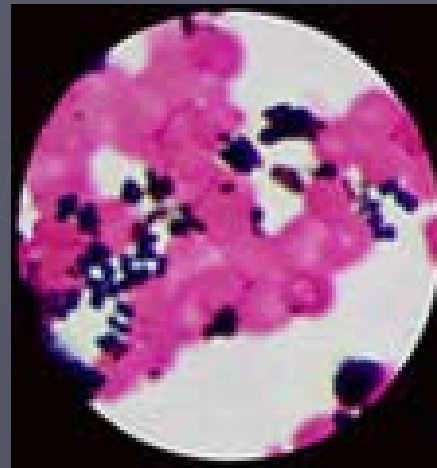
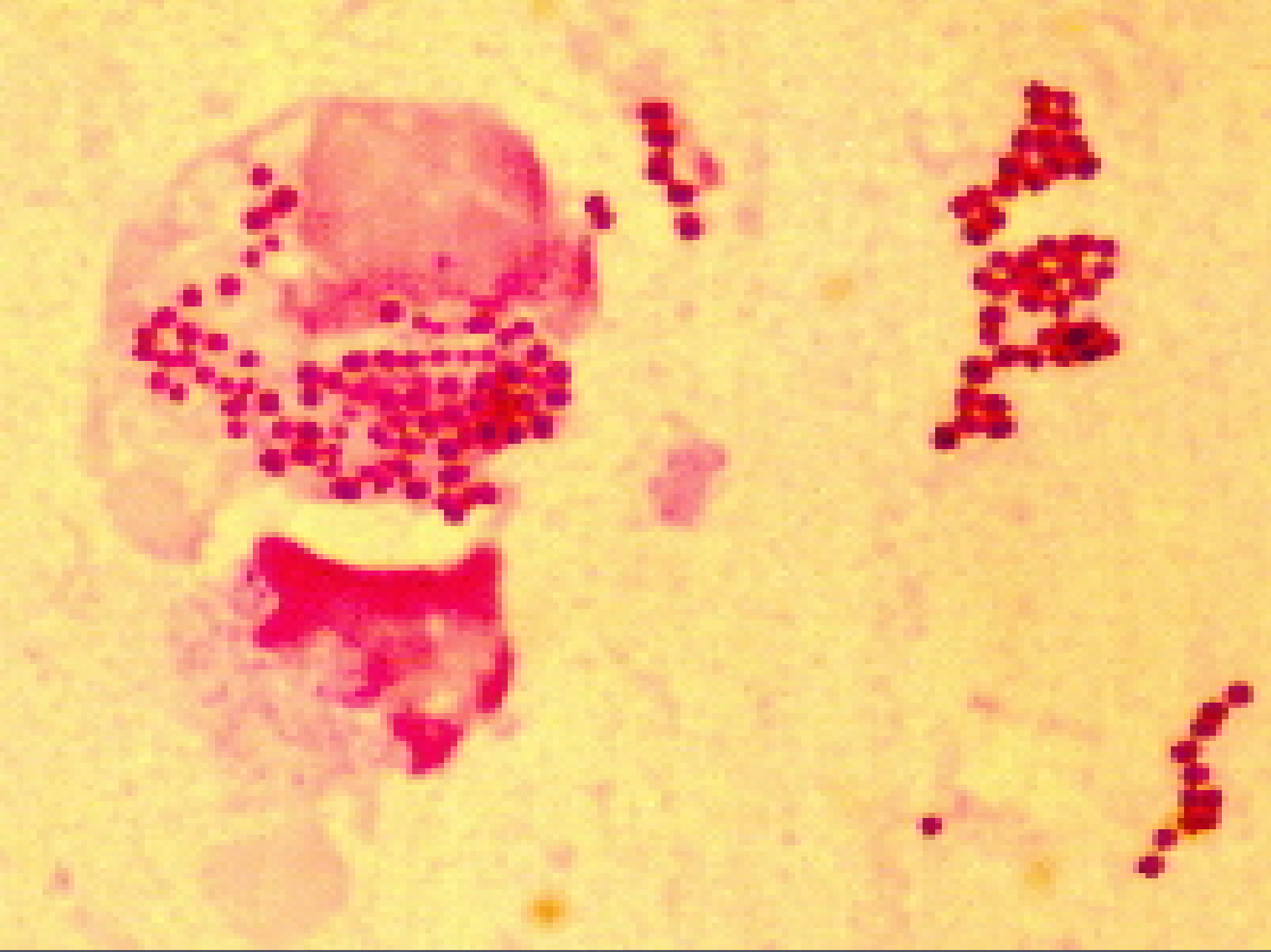


Les nouveaux traitements antistaphylococciques

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CLIN 2008

Les staphylocoques





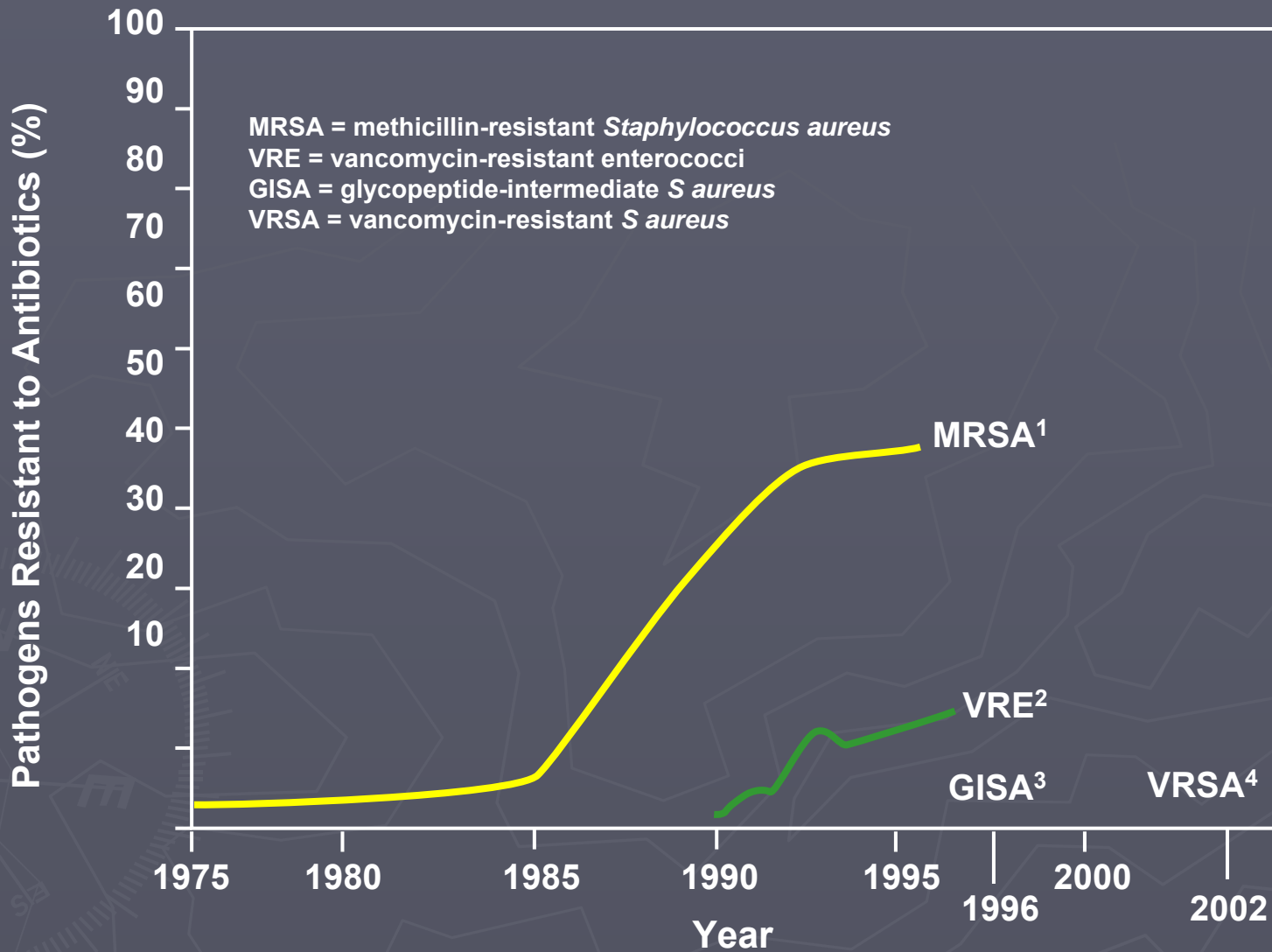




Les staphylocoques

▶ 1 - Introduction

- ▶ Les Staphylocoques sont des Cocci à Gram positif classiquement disposés en amas.
- ▶ Actuellement, on distingue 44 espèces.
- ▶ L'espèce *S. aureus* se distingue des staphylocoques appelés staphylocoques à coagulase négative (SCN) par la présence d'une coagulase.
- ▶ *S. aureus* est un germe très important aussi bien dans les infections communautaires que nosocomiales.

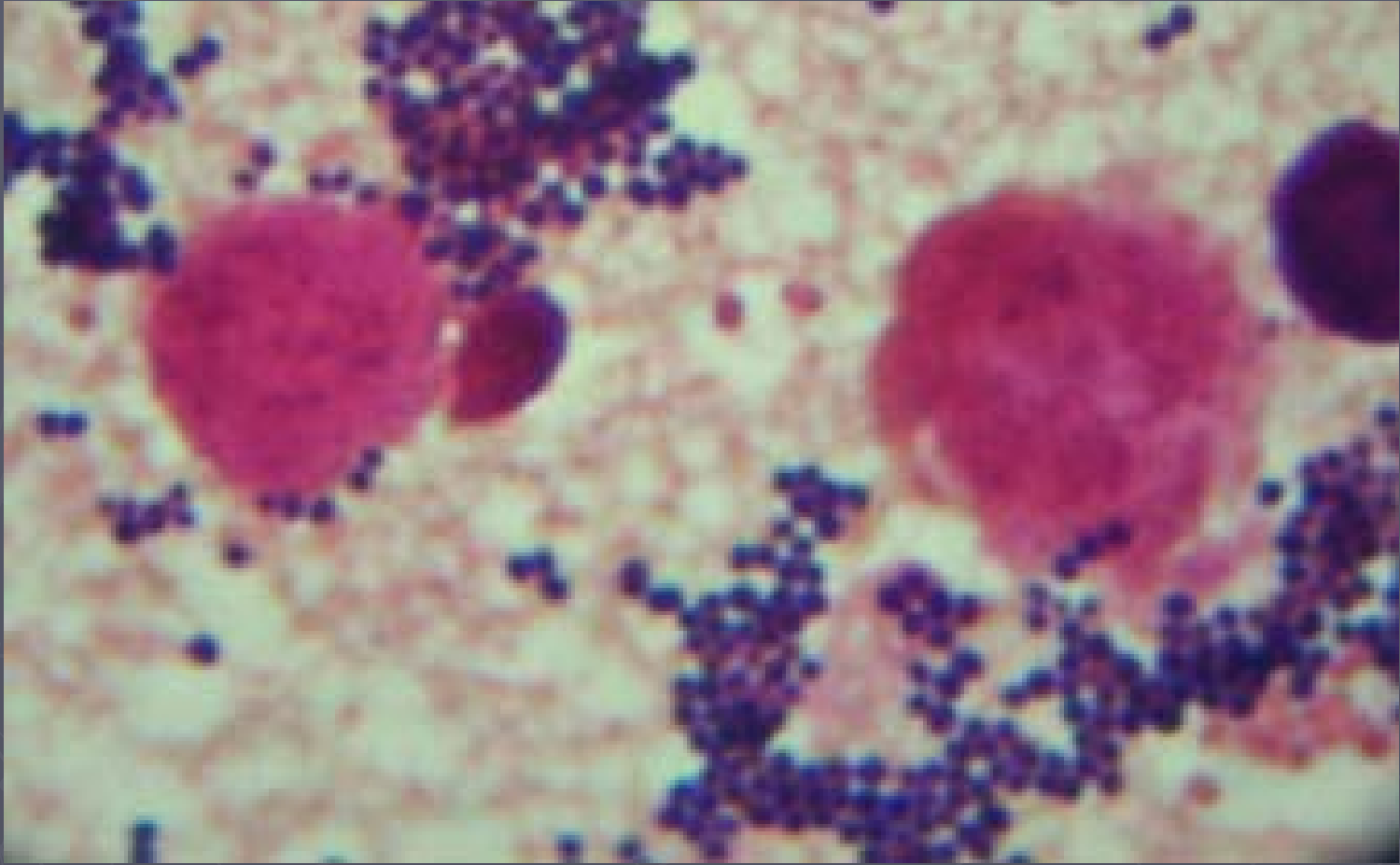


¹Smith TL et al. *N Engl J Med.* 1999;340:493-501. ²Martone WJ. *Infect Control Hosp Epidemiol.* 1998;19:539-545.

³Hiramatsu K et al. *J Antimicrob Chemother.* 1997;40:135-136. ⁴CDC. *MMWR Morb Mortal Wkly Rep.* 2002;51:565-567.

Pathogénécité

- ▶ Il est important de distinguer *S. aureus* des SCN. *S. aureus* a un potentiel de pathogénécité très important et est responsable aussi bien d'infections communautaires que nosocomiales.
- ▶ Par opposition, les **SCN** sont en règle générale des bactéries **opportunistes** essentiellement responsables d'infections nosocomiales.



En principe, les staph sont sensibles
aux

Pénicilline M: oxacilline (OXA)

Aminoglycosides: Gentamicine (GM)
Tobramycine (TM)

Macrolides : Erythromycine (E)

Synergistines: Pristinamycine (PRI)

Lincosamides: Clindamycine

Fluoroquinolones : Ciprofloxacin

Glycopeptides: Vancomycine (VAN)

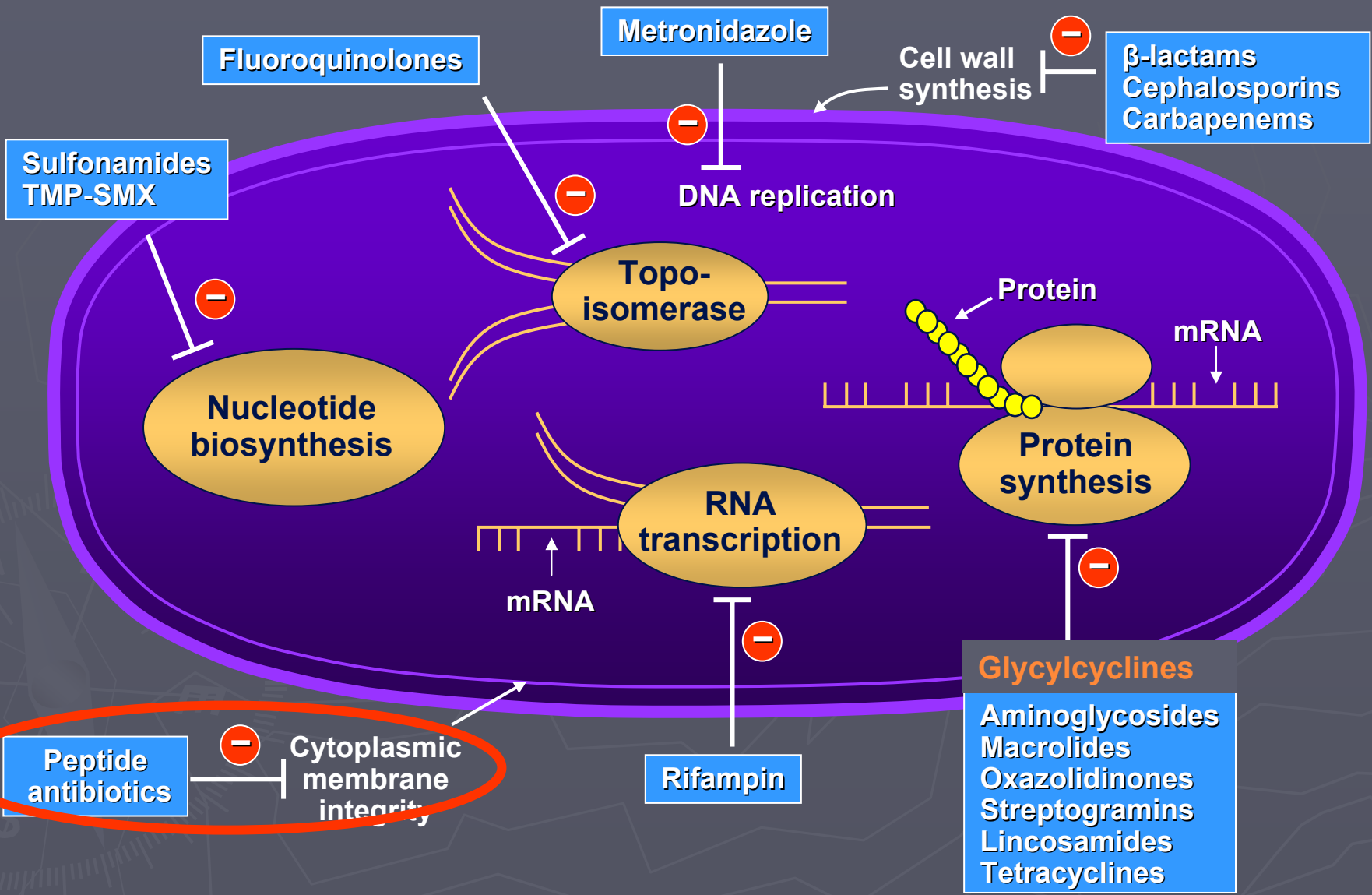
Rifampicine (RIF)

Acide fusidique (FA)

Fosfomycine (FOS)

Mais

- ▶ Résistance aux P A par pénicillinase
- ▶ Puis résistance aux P M par changement de PBP → SARM
- ▶ Puis résistance de type van ou par autres changement du peptidoglycane
- ▶ Résistance par changement de site intracellulaire



TMP-SMX = trimethoprim-sulfamethoxazole.

Daptomycin

► Description

- Cyclic lipopeptide indicated to treat complicated skin and skin structure infections caused by *S aureus* *Streptococcus pyogenes*, *Streptococcus* and *Enterococcus faecalis*.
- Binds to bacterial membranes and causes rapid membrane potential depolarization, thereby inhibiting protein, DNA, and RNA synthesis and ultimately causing cell death.

► Adult Dose

- 4 mg/kg IV q24h - q48h infused over 30 min

Pediatric Dose <18 years: Not established

► Interactions

- Coadministration with tobramycin slightly increases daptomycin C_{max} and AUC and decreases tobramycin C_{max} and AUC;

Daptomycin

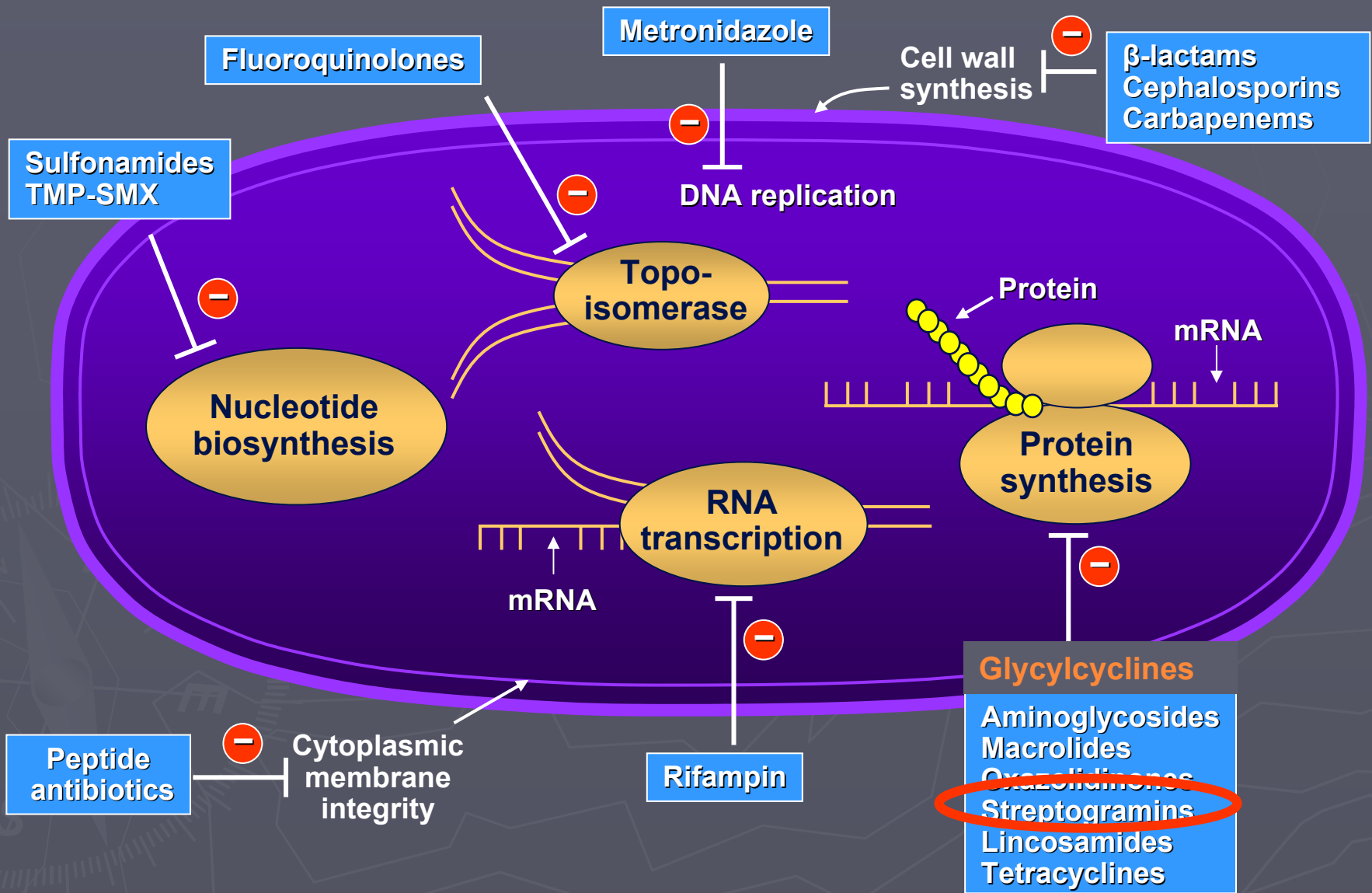
▶ Pregnancy

- B - Fetal risk not confirmed in studies in humans

▶ Precautions

- Decrease dose with renal function <30 mL/min; monitor CK levels and discontinue daptomycin with elevated CK and unexplained myopathy, not indicated for pneumonia (higher death rate in daptomycin-treated patients during phase III trials);

▶ not compatible with dextrose-containing solutions



TMP-SMX = trimethoprim-sulfamethoxazole.

Quinupristin/dalfopristin

► Description

- Belongs to the streptogramin group of antibiotics. Inhibits protein synthesis and is usually bacteriostatic.

► Adult Dose

- 7.5 mg/kg IV q8h

► Interactions

- **May** decrease elimination and **increase toxicity** of cyclosporine A, midazolam, nifedipine, terfenadine, astemizole, cisapride, alfentanil, alosetron, alprazolam, carbamazepine, delavirdine, diazepam, diltiazem, disopyramide, dofetilide, donepezil, erythromycin, ethinyl estradiol, felodipine, fexofenadine, indinavir, lidocaine, lovastatin, methylprednisolone, nevirapine, norethindrone, quinidine, ritonavir, saquinavir, simvastatin, tacrolimus, triazolam, trimetrexate, verapamil, vinblastine, and, possibly, other drugs

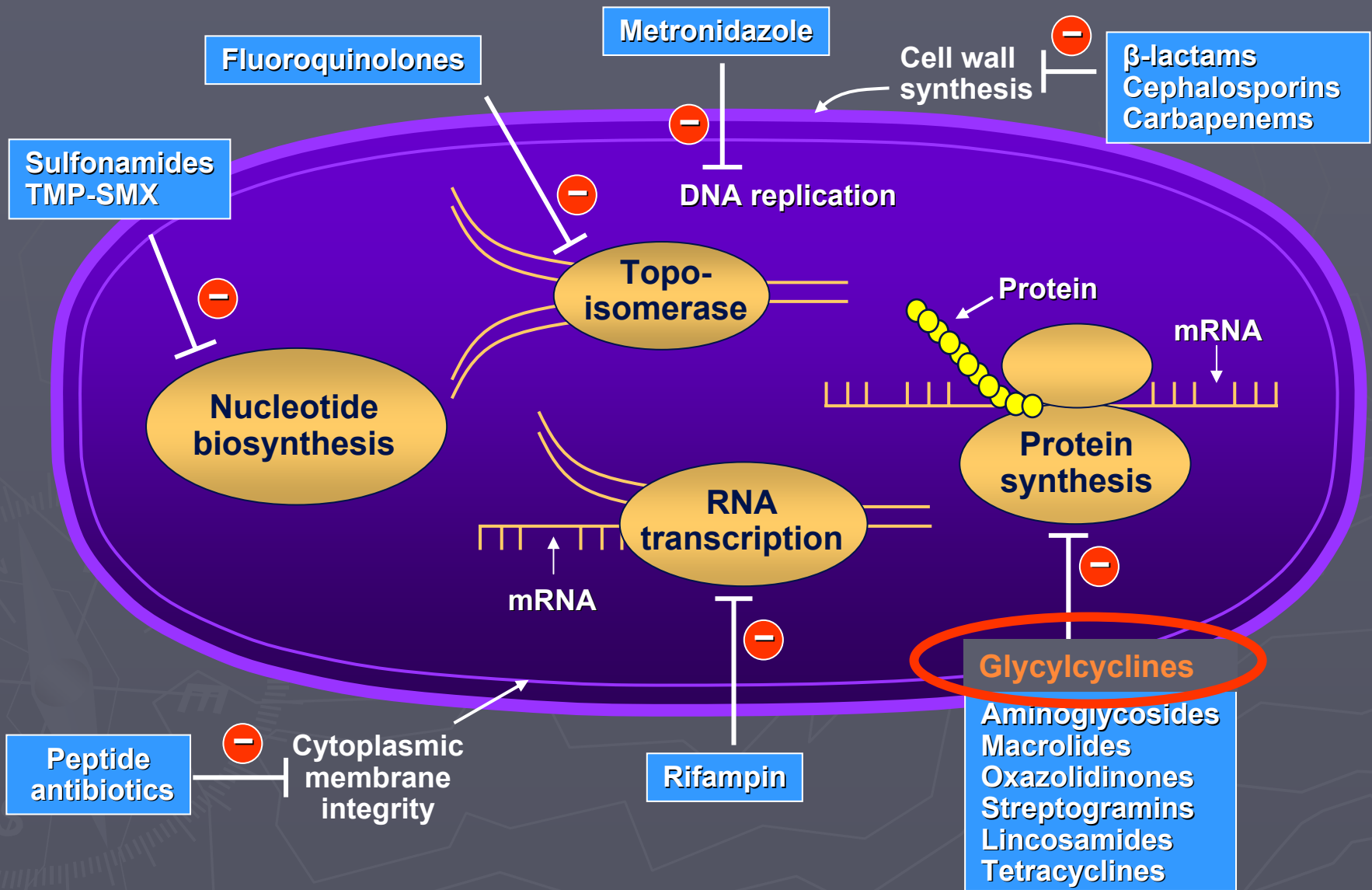
Quinupristin/dalfopristin

► Pregnancy

- C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

► Precautions

- Arthralgias and myalgias are common and may be severe; **venous irritation** common when administered through a peripheral line; administration through central venous line recommended; asymptomatic elevation of unconjugated bilirubin level may occur



TMP-SMX = trimethoprim-sulfamethoxazole.

Tigecycline

► Description

- A glycylycylcine antibiotic that inhibits bacterial protein translation by binding to 30S ribosomal subunit, and blocks entry of amino-acyl tRNA molecules in ribosome A site. Indicated for complicated skin and skin structure infections and complicated intra-abdominal infections.

► Adult Dose

- Infuse each dose over 30-60 min
100 mg IV once, then 50 mg IV q12h
Severe hepatic impairment (ie, Child Pugh class C):
100 mg IV once, then 25 mg IV q12h

► Pediatric Dose

- <18 years: Not established
>18 years: Administer as in adults

Tigecycline

► Interactions

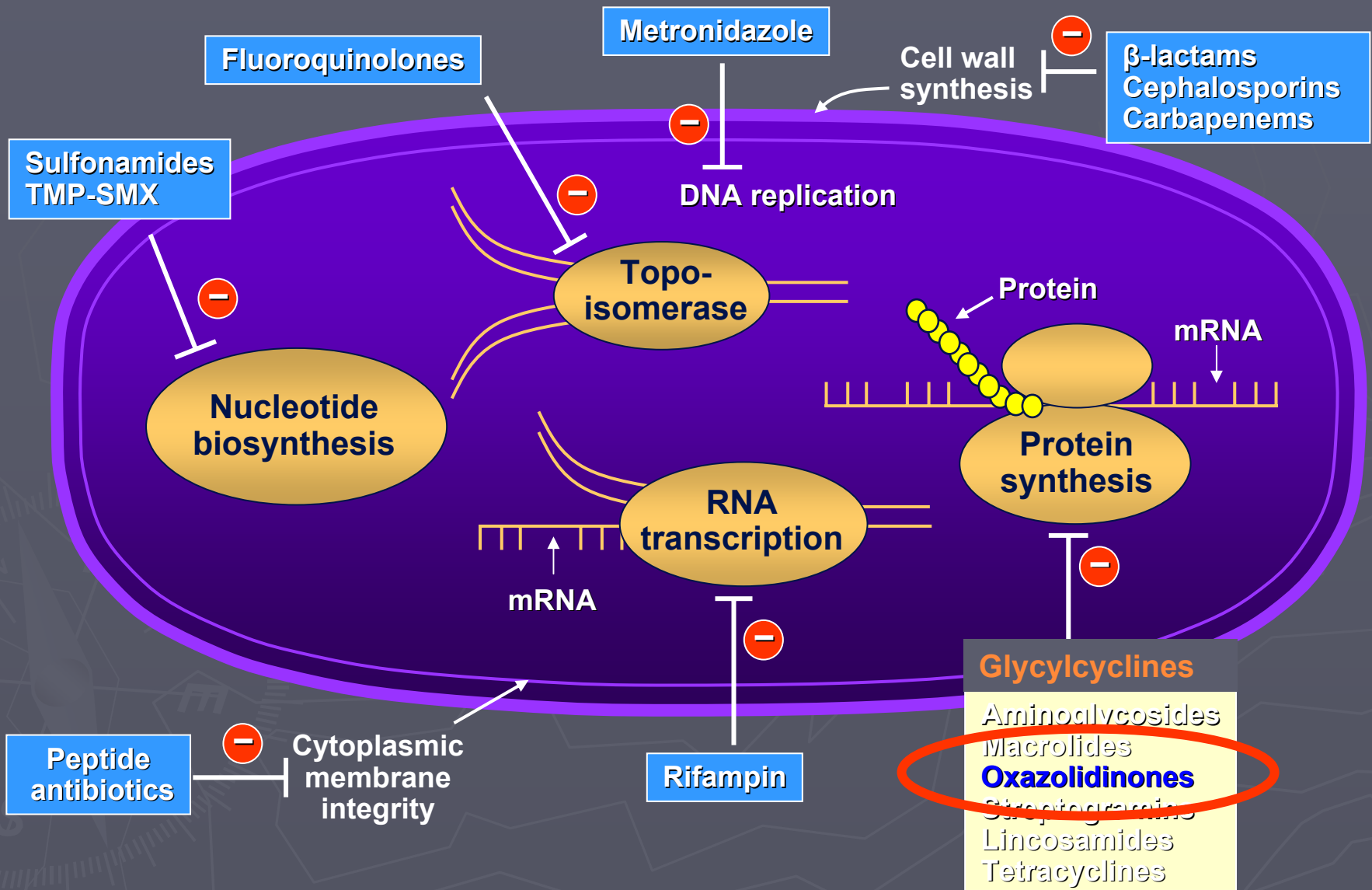
- Coadministration decreases warfarin clearance and **increases warfarin C_{max}** and AUC (monitor aPTT and INR); coadministration of antibiotics with oral contraceptives may decrease contraceptive effect

► Pregnancy

- D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

► Precautions

- Caution in severe hepatic impairment (reduce dose); may adversely effect tooth development; may permit clostridia overgrowth, resulting in antibiotic-associated colitis



TMP-SMX = trimethoprim-sulfamethoxazole.

Linezolid

► Description

- Prevents formation of functional 70S initiation complex. **Bacteriostatic** against staphylococci (MSSA/MRSA).

► Adult Dose

- 400-600 mg PO/IV q12h

► Interactions

- **May cause hypertension** when used concomitantly with adrenergic agents, including pseudoephedrine, sympathomimetic agents, vasopressors, or dopaminergic agents (reduce dose of dopamine or epinephrine if concurrent use required); serotonin syndrome may occur if used concomitantly with serotonergic agents, including TCAs, meperidine, dextromethorphan, trazodone, venlafaxine, and selective serotonin reuptake inhibitors

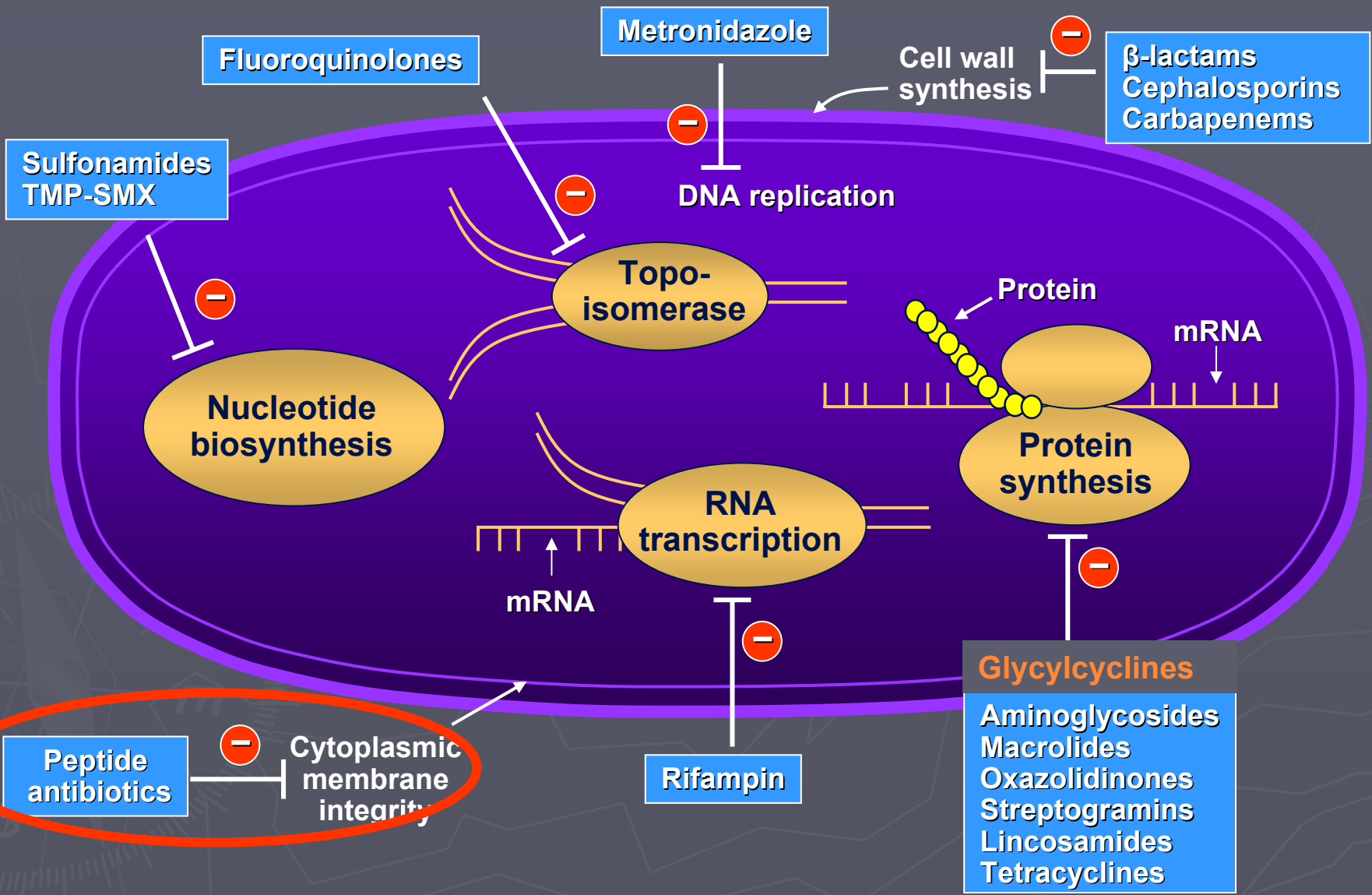
Linezolid

► Pregnancy

- C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

► Precautions

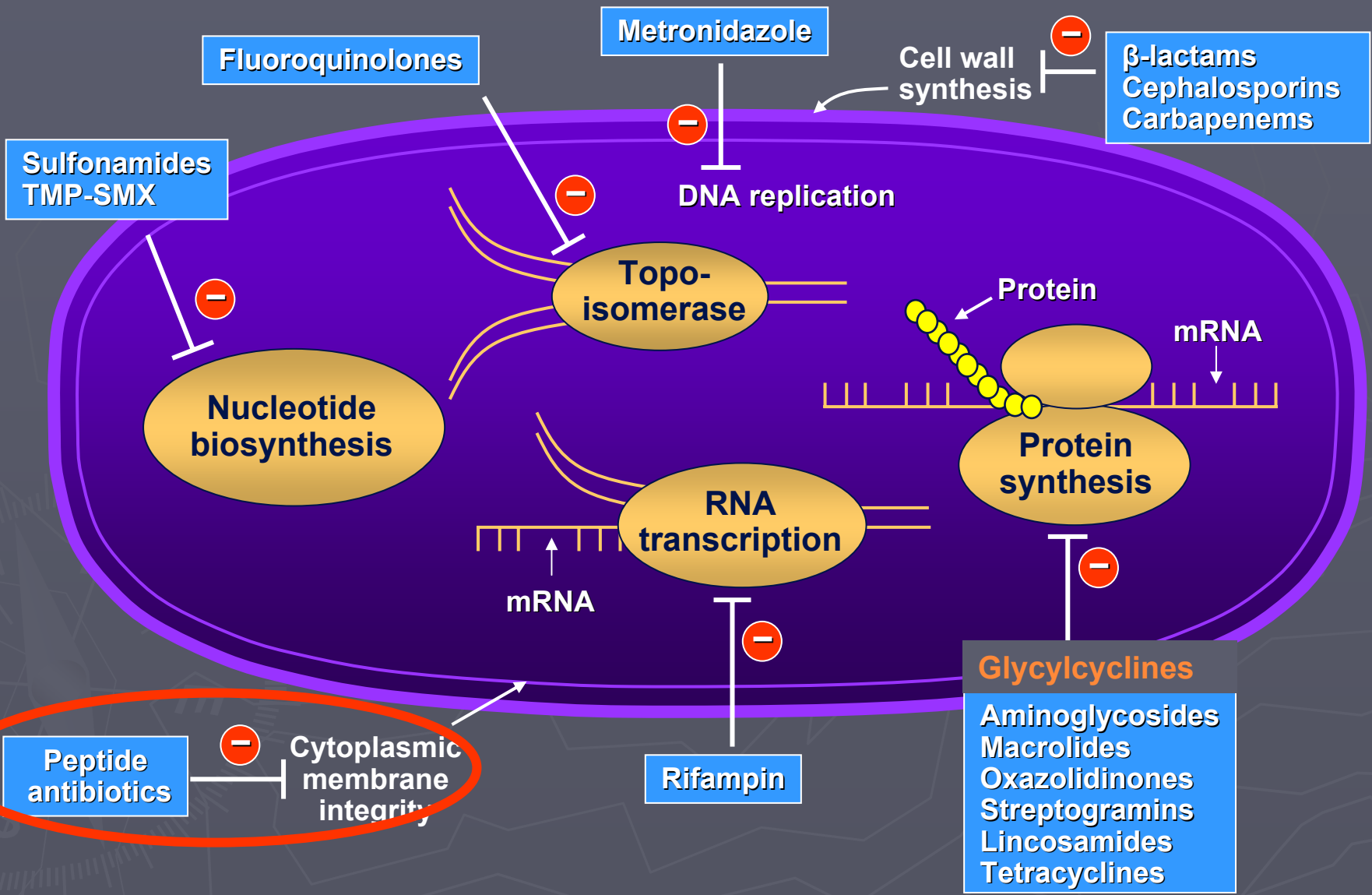
- Has mild MAOI properties and has interactions as other MAOIs; **caution in uncontrolled hypertension**, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism and in and patients who are at increased risk for bleeding, have preexisting thrombocytopenia, receive concomitant medications that may decrease platelet count or function, or who may require > 2 wk of therapy (**monitor platelet counts**); **unnecessary use may lead to development of resistance to drug**



TMP-SMX = trimethoprim-sulfamethoxazole.

Oritavancin

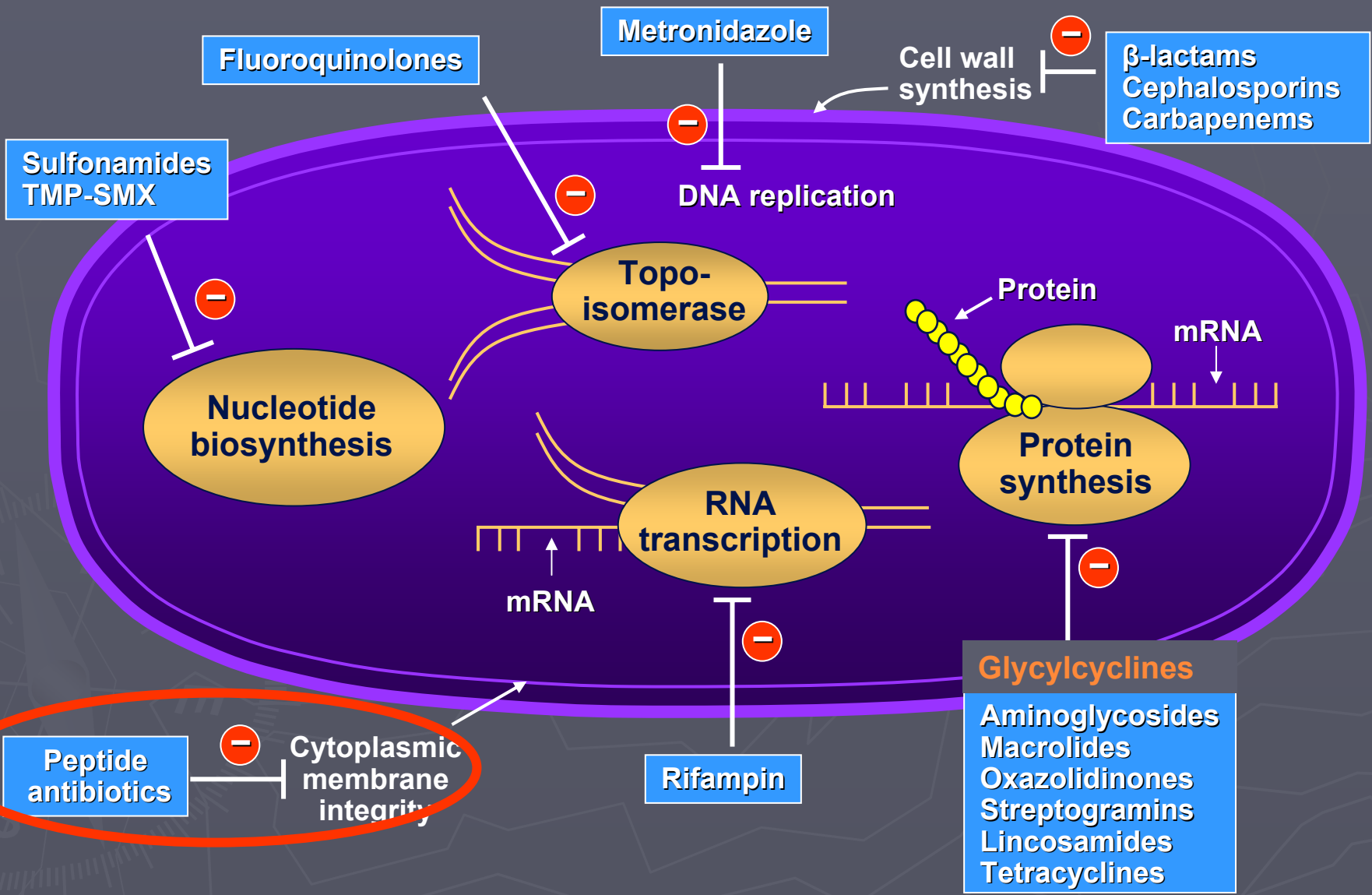
- ▶ Oritavancin is a **new** glycopeptide derived from vancomycin with excellent activity against MRSA and VISA/VRSA
- ▶ Results from a phase III trial evaluating oritavancin versus vancomycin–cephalexin in complicated skin and skin structure infections, show once again no statistically significant differences in outcomes between the two study groups.



TMP-SMX = trimethoprim-sulfamethoxazole.

Dalbavancin

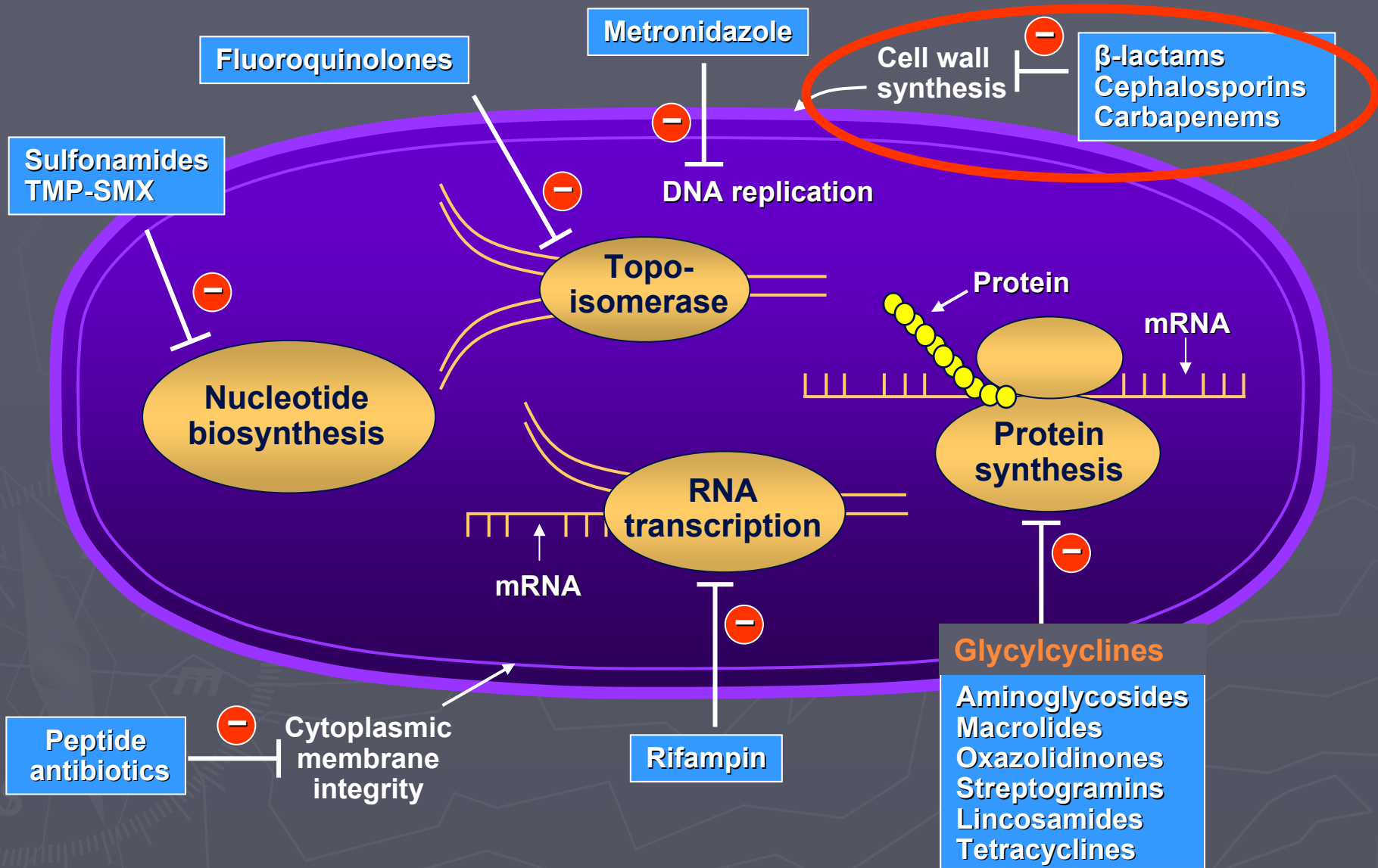
- ▶ Dalbavancin is another glycopeptide
- ▶ derived from teicoplanin with similar anti-staphylococcal activity as oritavancin.
- ▶ **It is characterized by a long half-life that allows a once a week dosage.**
- ▶ The results of a recent phase II trial on the efficacy of dalbavancin single dose versus vancomycin in catheter-related bacteremia by gram-positive pathogens, including MRSA, indicate a significantly higher overall success rate in patients receiving dalbavancin (87.0% versus 50.0%) which rises great expectations from the trials underway.



TMP-SMX = trimethoprim-sulfamethoxazole.

Telavancin

- ▶ Telavancin is a novel lipoglycopeptide with activity against gram-positive bacteria, including MRSA and VISA/VRSA
- ▶ A phase 2 clinical trial on the efficacy of telavancin once daily versus standard therapy in patients with MRSA in complicated skin and soft-tissue infections shows a clinical cure rate of 82% for telavancin versus 69% for the standard therapy.
- ▶ Microbiologic eradication in these patients was achieved in 84% for the telavancin and in 74% in the standard therapy group.
- ▶ Similar incidence and spectrum of adverse events was observed in the two groups.
- ▶ Telavancin is on current phase III trial in patients with hospital-acquired pneumonia.



TMP-SMX = trimethoprim-sulfamethoxazole.

Ceftobiprole

- ▶ Ceftobiprole (BAL9141) is a novel broad-spectrum parenteral cephalosporin with high affinity to PBP2, the methicillin-resistant determinant for beta-lactam resistance in **staphylococci**, and displays in-vitro activity against both MRSA and VRSA .
- ▶ In a rabbit model of endocarditis due to MRSA and VISA, ceftobiprole was as effective as vancomycin against MRSA and superior to vancomycin against VISA
- ▶ It is currently on trial in patients with hospital-acquired pneumonia and complicated skin and skin structure infections.

