Introduction to chemotherapy

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Chemotherapeutic drugs

- **antibacterial**
- antifungal
- antiviral
- antiparasitic
  - antiprotozoal
  - antihelminthic
- (cancer chemotherapy)
- (immunopharmacology)

antimicrobial

"provided the most dramatic examples of the advances of modern medicine"

BUT …

Introduction to antimicrobial chemotherapy

- **The focus**
  - **in microbiology**
    - pathogen isolation / identification
    - *in vitro* susceptibility: sensitive / resistant ?
    - (target identification)
  - **in pharmacology**
    - target identification / mechanism of action
    - clinical efficacy
    - effects on humans (adverse effects)
    - pharmacokinetics
      - "drug should reach its target"
      - dose/schedule optimization
    - drug interactions

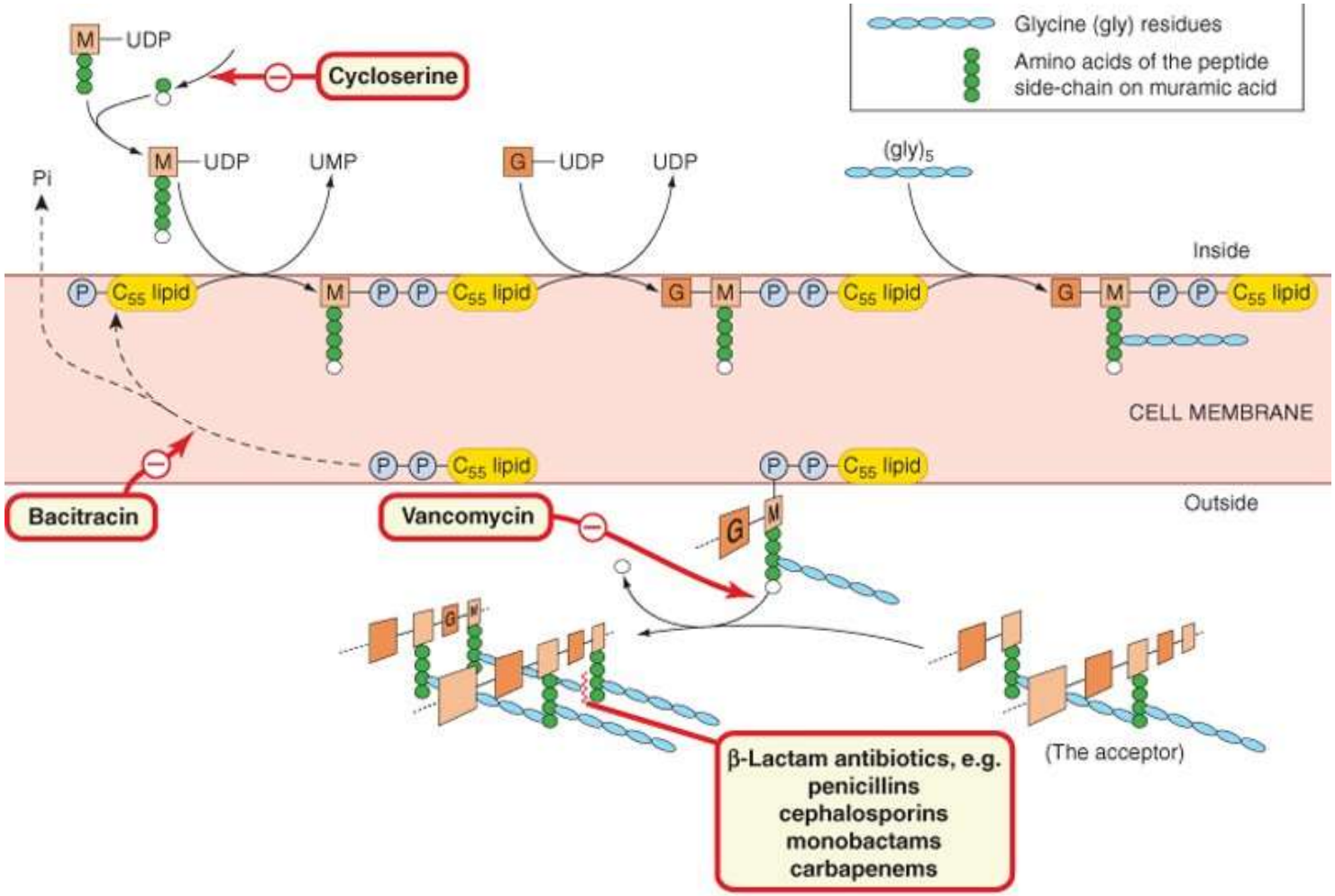
Antimicrobial drugs are used and prescribed by all physicians on a daily basis.

Basic concepts in antimicrobial chemotherapy

- pharmacophore
  - the active chemical moiety that binds to the **microbial receptor (target)**
- **selective toxicity**
  - bacteria ≠ viruses ≠ fungi ≠ parasites (≠ cancer cells)
- basis of selectivity
  - qualitative or quantitative biochemical differences
    - target **only** in the microorganisms – e.g. cell wall
    - target **more sensitive** in microorganisms – e.g. dihydrofolate reductase
- **selection of resistant microorganisms**

"target only in the microorganisms"

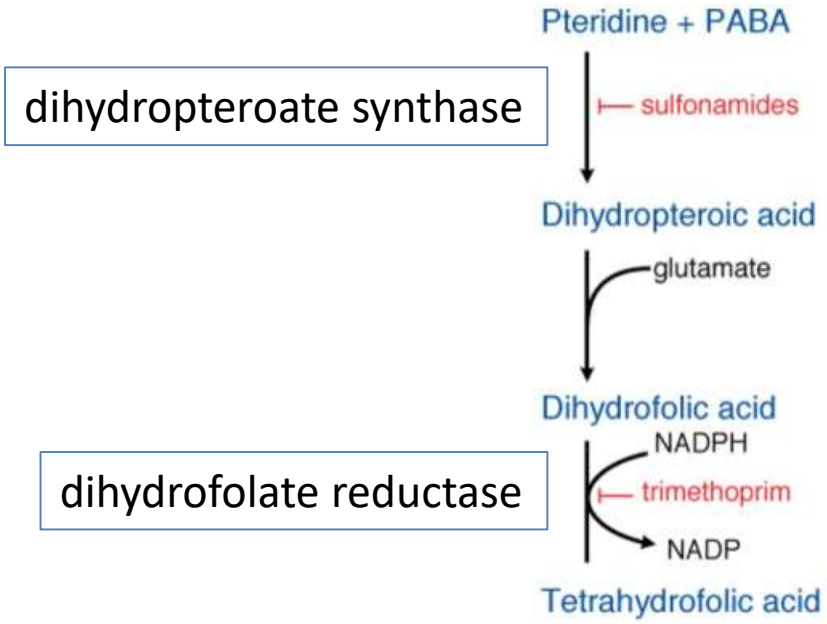
Mechanism of action of β-lactams



"target more sensitive"

Specificity of inhibitors of dihydrofolate reductase

inhibitor	IC_{50} (µmol/l) for dihydrofolate reductase		
	human	protozoal	bacterial
trimethoprim	260	0.07	0.005
pyrimethamine	0.7	0.0005	2.5
methotrexate	0.001	~0.1	inactive



Antimicrobial resistance

- **adaptation** to environmental pressure
- overuse and inappropriate use
  - significant **increase in rate** of resistance spread / induction
  - end of antibiotic era?
- resistance mechanisms
  - drug molecules could not reach their target
    - reduced entry - ↓ permeability (e.g. change in porins)
    - increased efflux (e.g. tetracyclines or *P falciparum*)
    - destruction of the antibiotic (e.g. β-lactams, aminoglycosides)
  - alteration of target (e.g. PBP in MRSA, target modification)

Most common errors promoting antimicrobial resistance

- inappropriate use (misuse)
  - e.g. antibacterial drugs for viral infections
  - use of antibiotics in animal husbandry
- treatment of fever of unknown origin
- under dosing
  - selection of resistant subpopulation
- avoidance of other therapeutic methods
  - abscess, permanent catheter, foreign body
- absence of correct bacteriological information

Singnificance of resistance (2012)

- In Preface of "Goodman & Gilman's The Pharmacological Basis of therapeutics, 12th edition, 2011":
  - "The process of editing brings into view many remarkable facts, theories and realizations. **Three stand out**: … **the development of resistance to antimicrobial agents**, mainly through their overuse in medicine and agriculture, **threatens to return us to the pre-antibiotic era.**"
- And this book is **NOT** focused on chemotherapy

Singnificance of resistance (2013)

THIS WEEK

The antibiotic alarm

There is a growing recognition that action must be taken to deal with the alarming rise in the incidence of bacteria resistant to today's antibiotics, and its implications for global health.

that the message is being heard.

This week saw the launch of a UK report into infections and the rise of antimicrobial resistance from Sally Davies, the UK chief medical officer. The report draws on the expertise of academics and health-care professionals to outline the burden of infectious disease in the United Kingdom and the increasing proportion of infections due to antibiotic-resistant strains. Davies makes 17 recommendations for policy and political action relating to antibiotic resistance, pathogen surveillance, prevention of infection and training for the health-care workforce. Chief among these recommendations is that antibiotic resistance should be added to the UK government's list of threats to national security, alongside pandemic influenza and terrorism, a recommendation alone that is sure to raise the profile

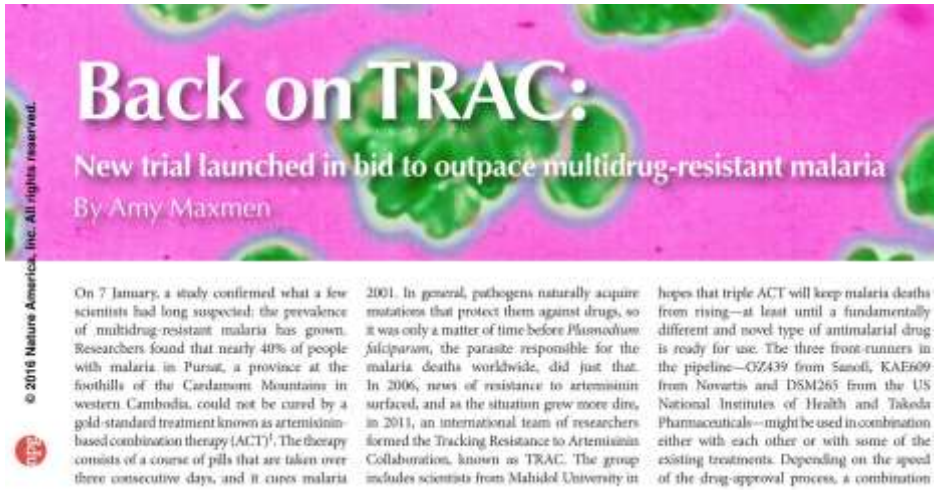
Singnificance of resistance (2016)

Comment

Colistin resistance: a major breach in our last line of defence

In hospital practice, clinicians have been buoyed by the recent development of new antibiotics active against multidrug resistant Gram-negative bacilli. However, recently approved antibiotics like ceftazidime-avibactam or ceftolozane-tazobactam do not provide activity against all Gram-negative bacilli, with notable gaps in their coverage, including the notorious New Delhi metallo-β-lactamase 1-producing organisms and many strains of carbapenem resistant *Acinetobacter baumannii*. For this reason, the polymyxins (colistin and polymyxin B) remain the last line of defence against many Gram-negative bacilli. Colistin-resistant and even pan-drug-resistant Gram-negative bacilli have already been reported.[1,2] Typically, colistin resistance is due to chromosomally mediated modulation

Liu and colleagues[3] present data from China showing that *E coli* from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in *E coli* and *K pneumoniae* isolates from Chinese patients in hospital. These findings suggest that the links between agricultural use of colistin, colistin resistance in slaughtered animals, colistin resistance in food, and colistin resistance in human beings are now complete. One of the few solutions to uncoupling these connections is limitation or cessation of colistin use in agriculture. This will require substantial political will and we call upon Chinese leaders to act rapidly and decisively. Failure to do so will create a public health problem of major dimensions.



Back on TRAC:

New trial launched in bid to outpace multidrug-resistant malaria

By Amy Maxmen

On 7 January, a study confirmed what a few scientists had long suspected: the prevalence of multidrug-resistant malaria has grown. Researchers found that nearly 40% of people with malaria in Pursat, a province at the foothills of the Cardamom Mountains in western Cambodia, could not be cured by a gold-standard treatment known as artemisinin-based combination therapy (ACT)[1]. The therapy consists of a course of pills that are taken over three consecutive days, and it cures malaria

2001. In general, pathogens naturally acquire mutations that protect them against drugs, so it was only a matter of time before *Plasmodium falciparum*, the parasite responsible for the malaria deaths worldwide, did just that. In 2006, news of resistance to artemisinin surfaced, and as the situation grew more dire, in 2011, an international team of researchers formed the Tracking Resistance to Artemisinin Collaboration, known as TRAC. The group includes scientists from Mahidol University in

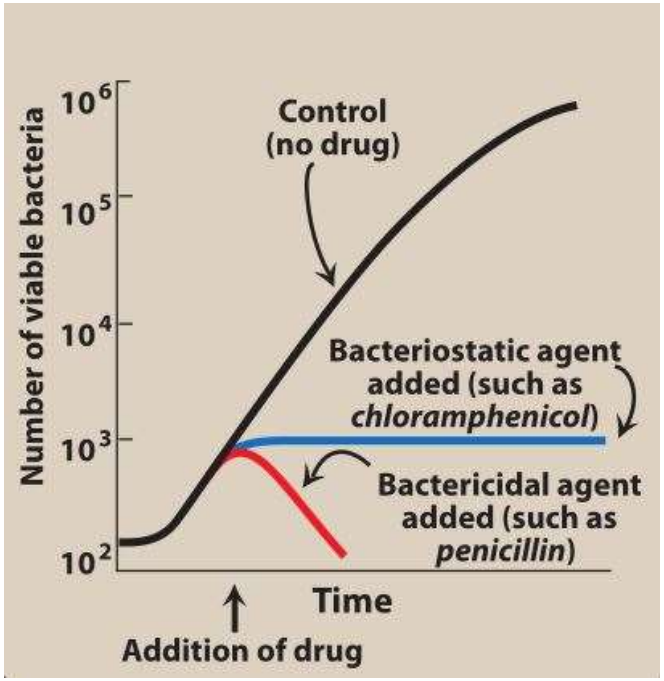
hopes that triple ACT will keep malaria deaths from rising—at least until a fundamentally different and novel type of antimalarial drug is ready for use. The three front-runners in the pipeline—OZ439 from Sanofi, KAE609 from Novartis and DSM265 from the US National Institutes of Health and Takeda Pharmaceuticals—might be used in combination either with each other or with some of the existing treatments. Depending on the speed of the drug-approval process, a combination

"**plasmid-mediated colistin resistance** for the first time"
"**readily passed** between Escherichia coli strains"
"the plasmid could be passed to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* strains"

"It therefore seems inevitable that plasmid-mediated transfer of colistin resistance **will seriously limit the lifespan of the polymyxins** as the backbone of regimens against multiply resistant Gram-negative bacilli."

"On 7 January, a study confirmed what a few scientists had long suspected: the prevalence of **multidrug-resistant malaria** has grown. Researchers found that nearly **40% of people with malaria** in Pursat, a province at the foothills of the Cardamom Mountains in western Cambodia, **could not be cured by a gold-standard treatment** known as artemisinin-based combination therapy."

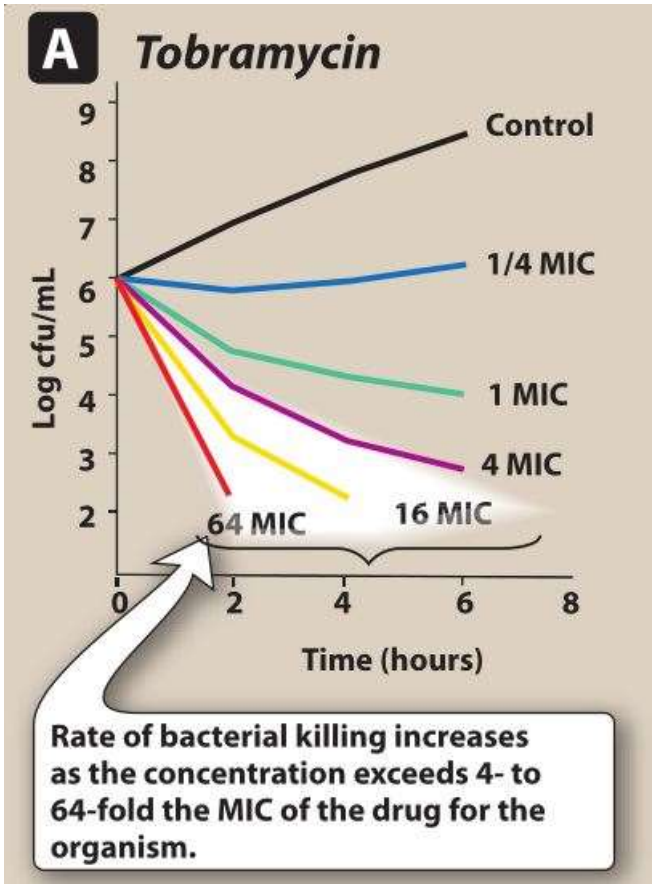
Bacteriostatic versus bactericidal activity

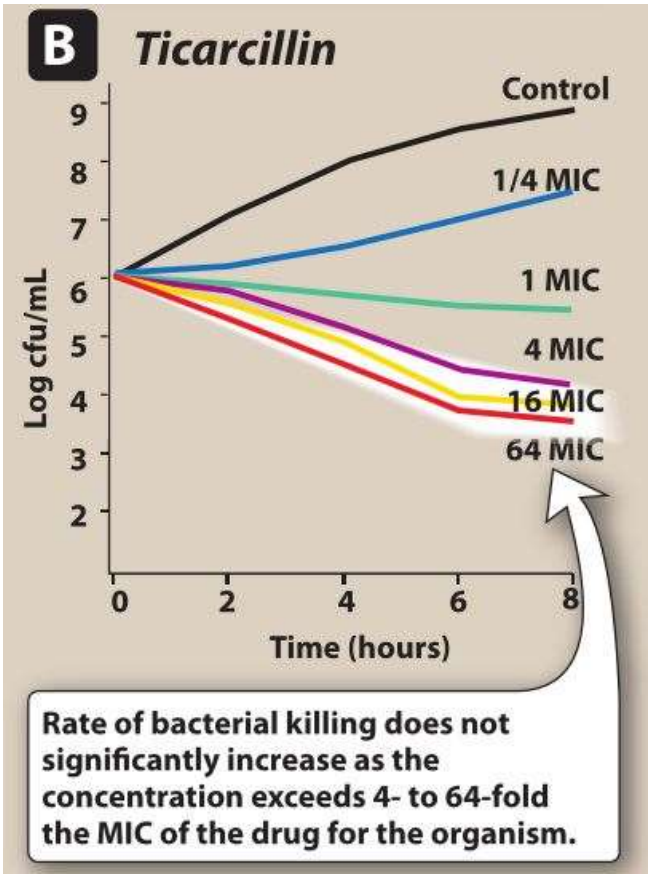


bactericidal	bacteriostatic
aminoglycosides	chloramphenicol
β-lactams	macrolides
vancomycin	sulfonamides
metronidazole	tetracyclines
fluoroquinolones	tigecycline
rifampin	oxazolidinones
isoniazid	clindamycin

- MIC = minimum inhibitory concentration
- MBC = minimum bactericidal concentration
- value of “cidal” – “static” classification is limited
  - can be bactericidal against selected organisms – e.g. chloramphenicol
  - enterococci only inhibited and not killed by – vancomycin, penicillin, ampicillin
- compromised host defense (e.g. endocarditis, neutropenia) → bactericidal

Concentration dependent vs. time dependent killing

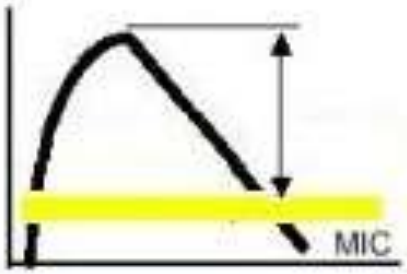




but MIC should be considered …

Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

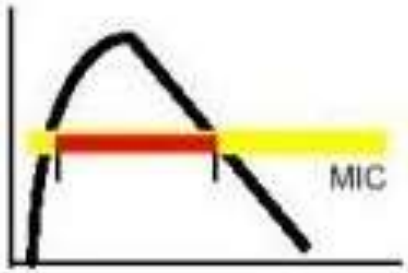
Peak/MIC



aminoglycosides
rifampin (but toxic)

cc dependent

T > MIC



β-lactams
5-fluorocytosine

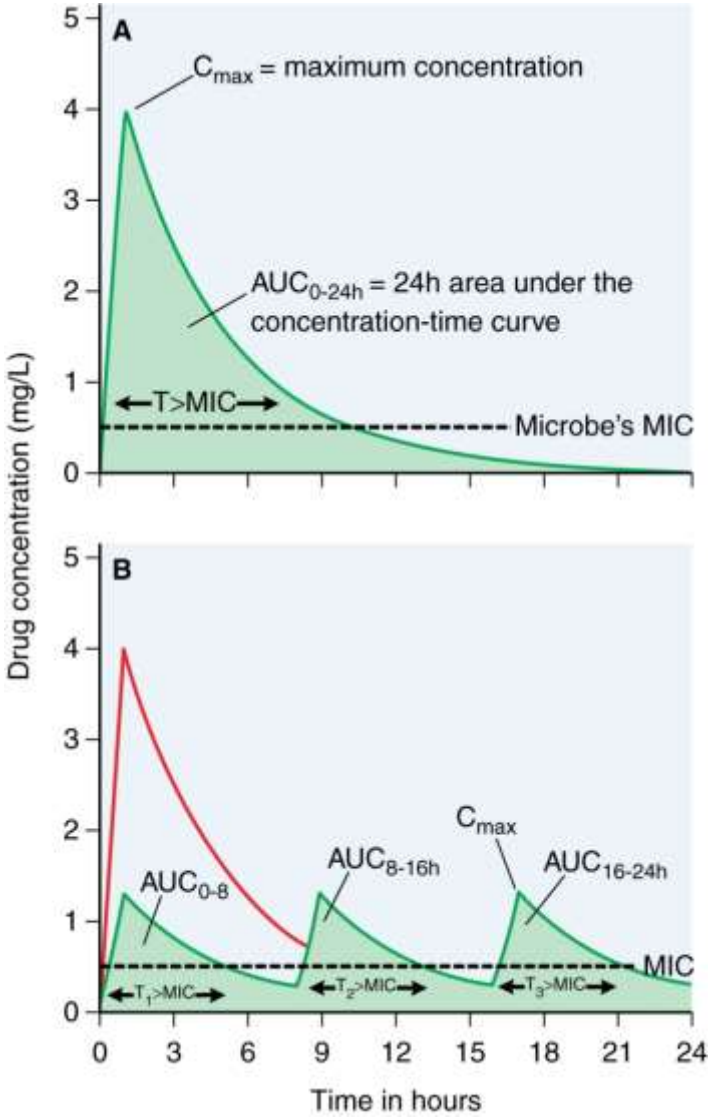
time dependent

24h-AUC/MIC

daptomycin

"AUC" dependent

Effect of the shape of the drug C_p vs. time curve



- drug exposition should be compared to **MIC value (**sensitivity → clinical success)
- an optimal dose → at least IC_{80}-IC_{90} **at the site of infection**
- in vitro – static cc ↔ in patients – dynamic cc
- the optimal antimicrobial effect depends on the **shape of the concentration-time curve**
- the **shape** of the curve (C_{max} , AUC and T>MIC) can **influence** not only the effect but the **toxicity** (and **resistance** induction!) too

CONCLUSION:
dose, route and administration schedule is important

Postantibiotic effect

- limited exposure – persistent growth inhibition
- PAE = T – C (*in vitro*)
  - T: time for 10x increase in test
  - C: time for 10x increase in control
- mechanisms
  - slow recovery after non-lethal damage
  - drug persistence
  - new enzyme synthesis

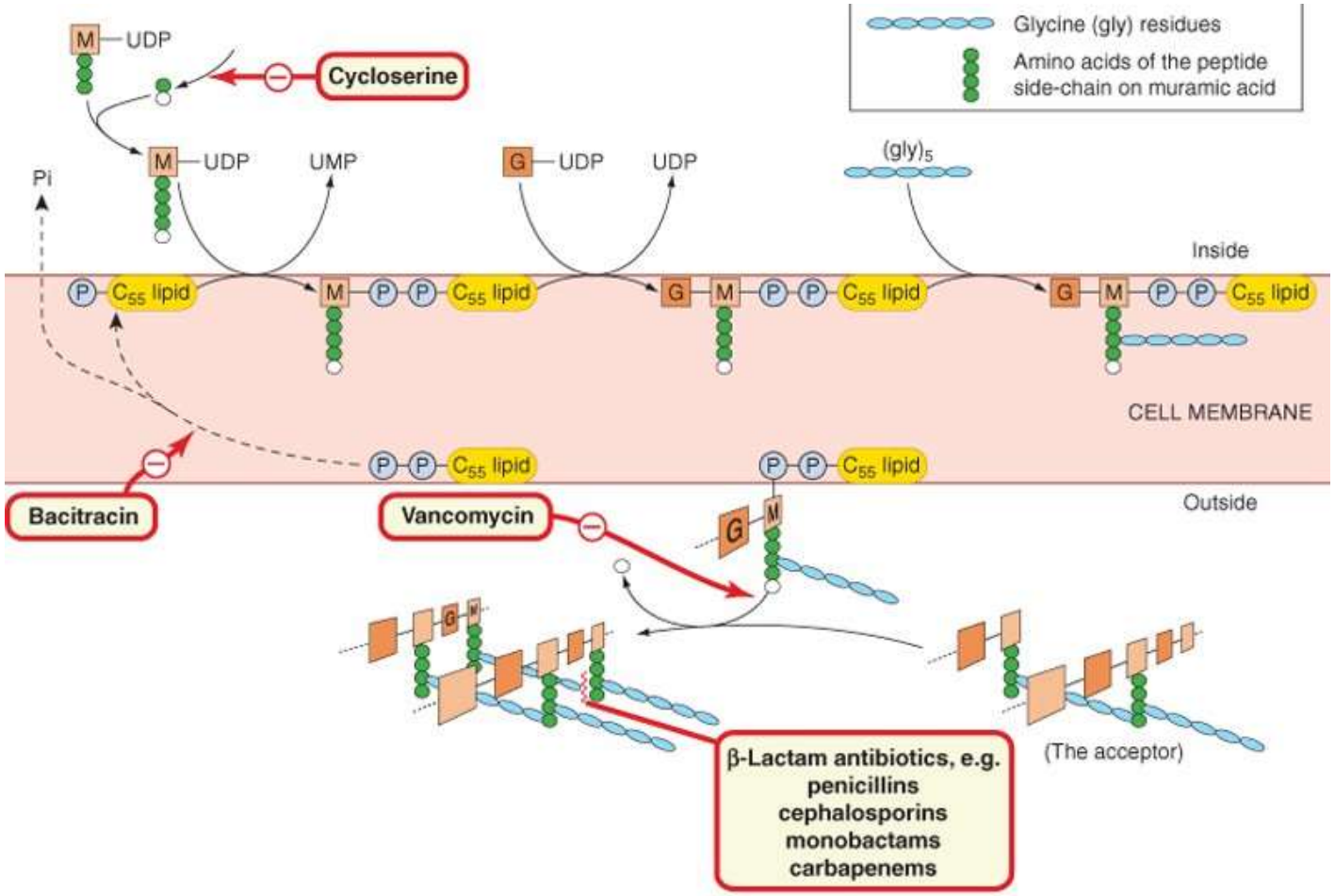
examples of *in vitro* PAE ≥ 1.5 hours

against G+ cocci	against G- bacilli
penicillins	carbapenems
cephalosporins	**aminoglycosides**
carbapenems	tetracyclines
sulfonamides	chloramphenicol
vancomycin	quinolones
trimethoprim	**rifampin**

Overview of potential targets of chemotherapy

- peptidoglycan (cell wall synthesis)
- ribosomes (protein synthesis)
- nucleotide/nucleic acid synthesis and processing
  - antimetabolites
    - folate metabolism
    - pyrimidine and purine analogs
  - topoisomerase (DNA gyrase)
  - DNA polymerase
- other formed cell structures
  - cell membrane
  - microtubules

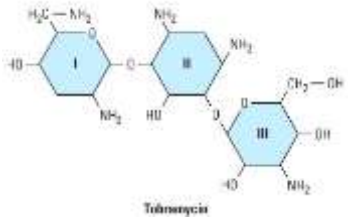
Peptidoglycan (cell wall) synthesis



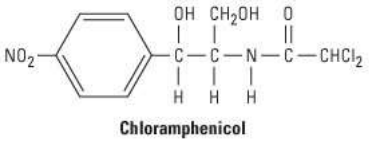
Protein synthesis 1.

	R_7	R_6	R_5	Renal Clearance (mL/min)
Chlortetracycline	—Cl	—CH_3	—H	35
Oxytetracycline	—H	—CH_3	—OH	90
Tetracycline	—H	—CHG	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	=CH_2*	—OH	31
Doxycycline	—H	—CH_3*	—OH	15
Minocycline	—$N(CH_3)_2$	—H	—H	10

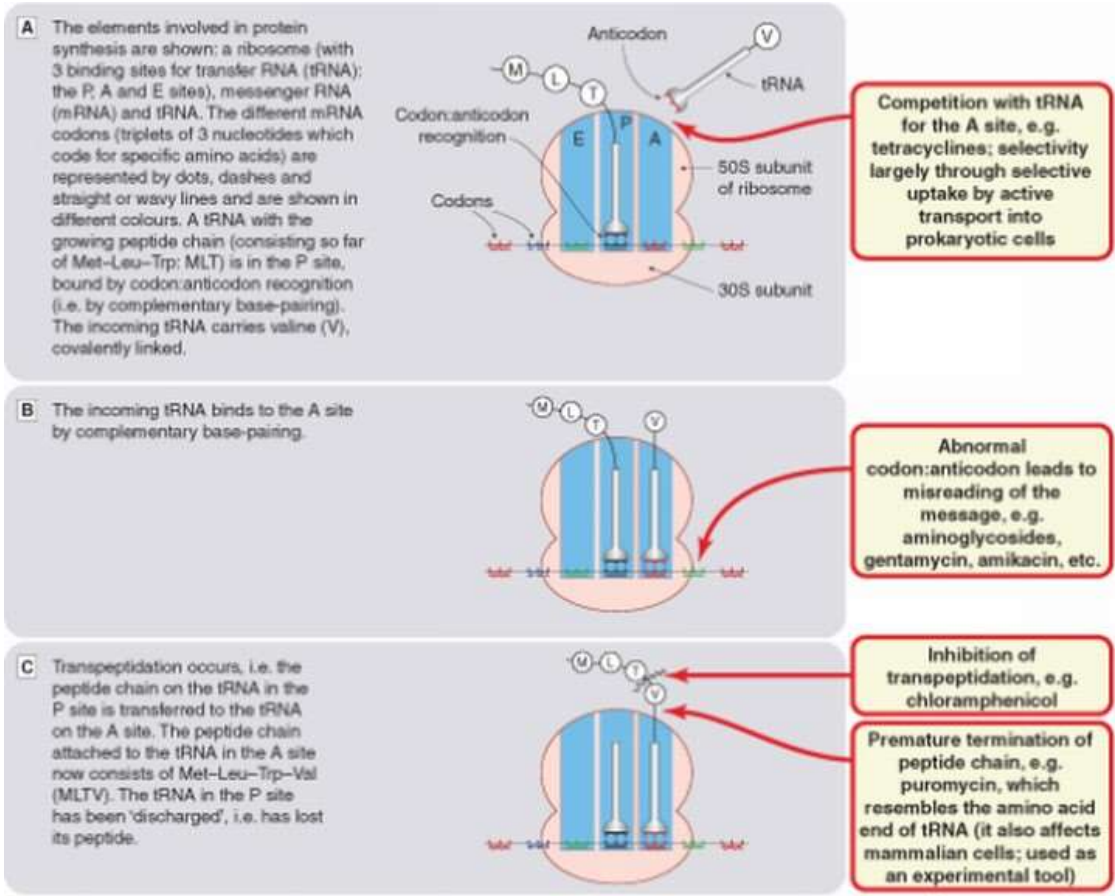
*There is no —OH at position 6 on methacycline and doxycycline.



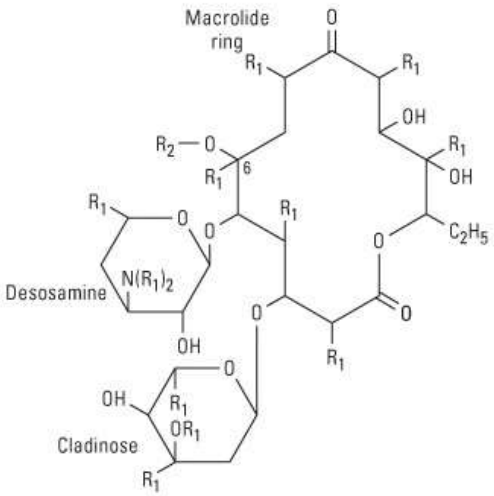
Tobramycin



Chloramphenicol

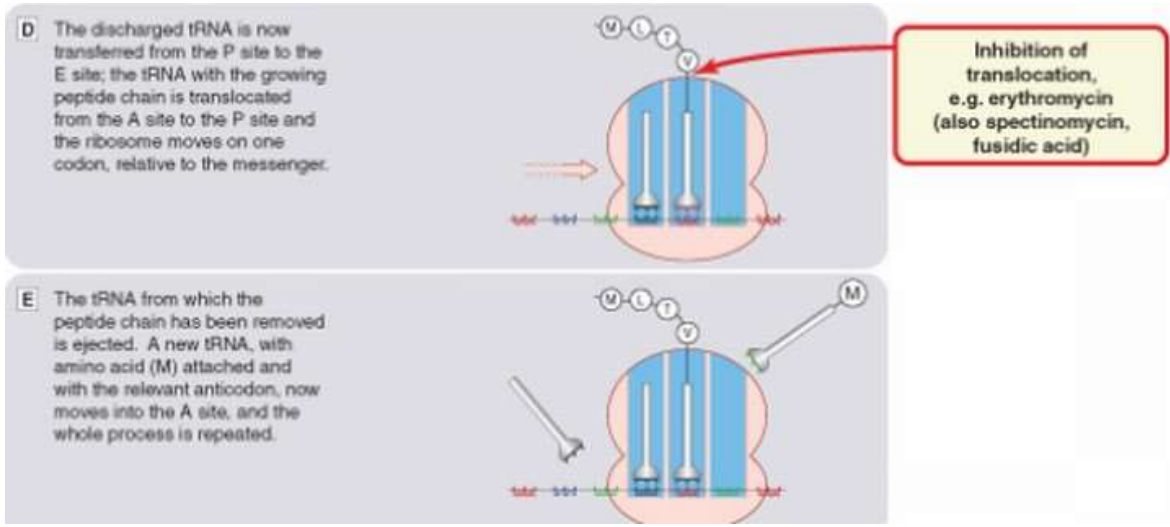


Protein synthesis 2.



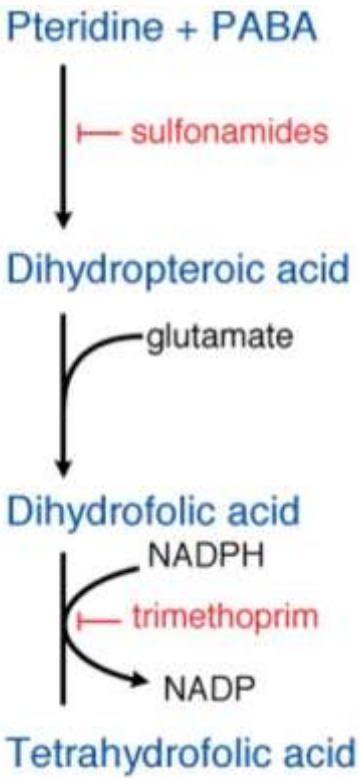
Erythromycin ($R_1 = CH_3$, $R_2 = H$)

Clarithromycin (R_1, $R_2 = CH_3$)



Folate

dihydropteroate synthase



sulfamethoxazole
sulfadoxin

dihydrofolate reductase

trimethoprim
pyrimethamine

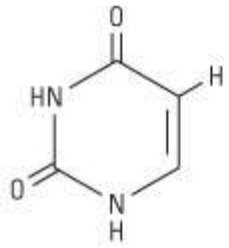
sequential blockade

- sulfamethoxazole + trimethoprim = co-trimoxazole – bacteria (e.g. UTI or *P. jiroveci*)
- sulfadoxine + pyrimethamine = Fansidar® – malaria (*P. falciparum*), **now resistance**!

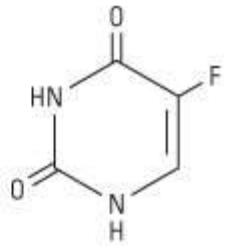
Pyrimidine and purine analogs

(examples only)

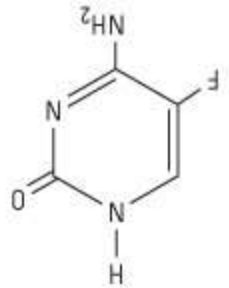
- pyrimidine
  - 5-fluorouracil – cancer
  - flucytosine – antifungal
- purine
  - 6-mercpatopurine – cancer
  - thioguanine – cancer



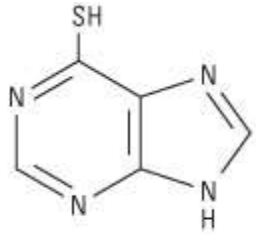
Uracil



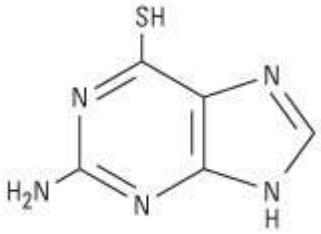
5-FU



Flucytosine



6-Mercaptopurine



6-Thioguanine

Nucleic acid synthesis

- DNA or RNA polymerase inhibition
  - rifampin – tuberculosis
  - acyclovir – HSV
  - zidovudine – HIV
- topoisomerase II (DNA gyrase) and IV inhibition
  - quinolones / fluoroquinolones
    - ciprofloxacin / levofloxacin / moxifloxacin
- direct effects on DNA
  - alkylating agents – cancer
    - cyclophosphamide

Cell structures

- membrane
  - polymixins – G- bacteria
  - daptomycin – G+ bacteria
  - amphotericin-B – antifungal
- microtubules
  - albendazole – antihelminthic
  - vinblastine / vincristine – cancer
  - paclitaxel / docetaxel – cancer