Antibacterial drugs: General Principals

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- **Antibacterial drugs** - natural or synthetic drugs, that either selectively inhibit the growth of bacteria or kill bacteria

- **Antibiotics** - substances produced by microorganisms and causing growth inhibition or death of other microorganisms.

The magic bullet concept

developed by a German Nobel laureate P. Ehrlich


Paul Ehrlich

In 1900 Ehrlich formed an idea that it could be possible to kill bacteria without harming the body itself.

Antibacterial drugs origin

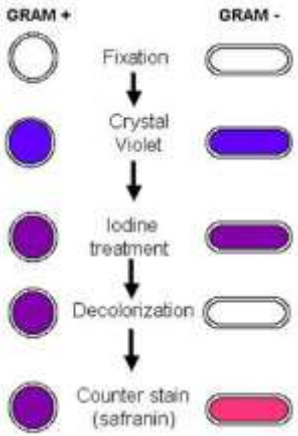
- Natural (*e.g. benzylpenicillin*)
- Semi-synthetic (*e.g. amoxicillin*)
- Synthetic (sulfonamides, fluoroquinolones)

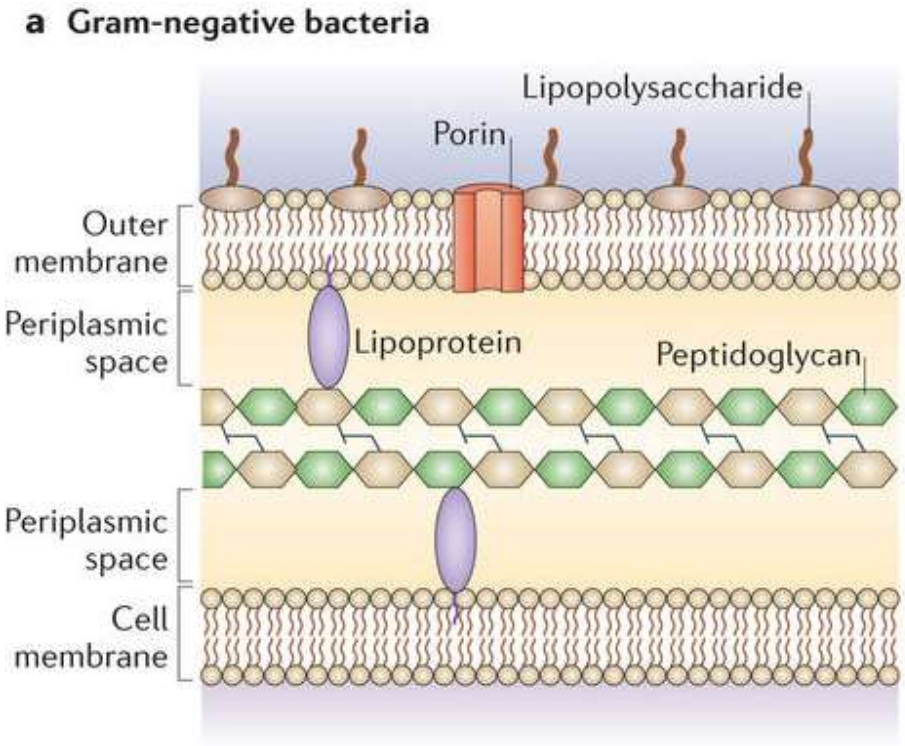
Chemotherapeutic spectra

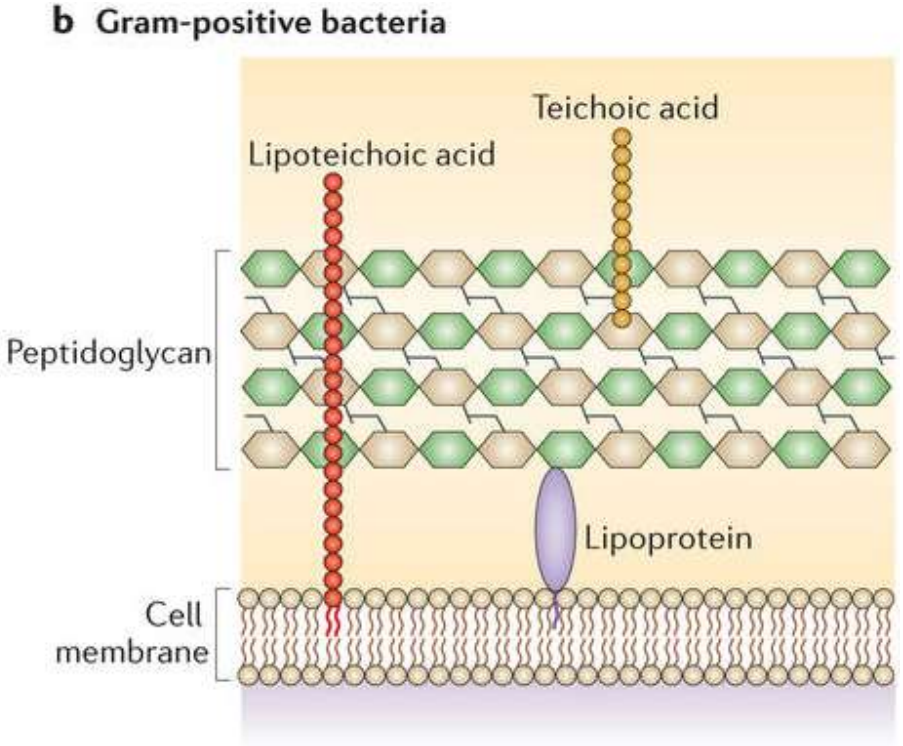
- **Narrow-spectrum** chemotherapeutic agents acting only on a single or a limited group of microorganisms (*isoniazid* is active only against Mycobacterium tuberculosis)

- **Extended or Broad spectrum chemotherapeutic agents** can be effective against gram-positive and also gram-negative bacteria

Hans Christian Joachim Gram (1884 g.)







Type of antibacterial action

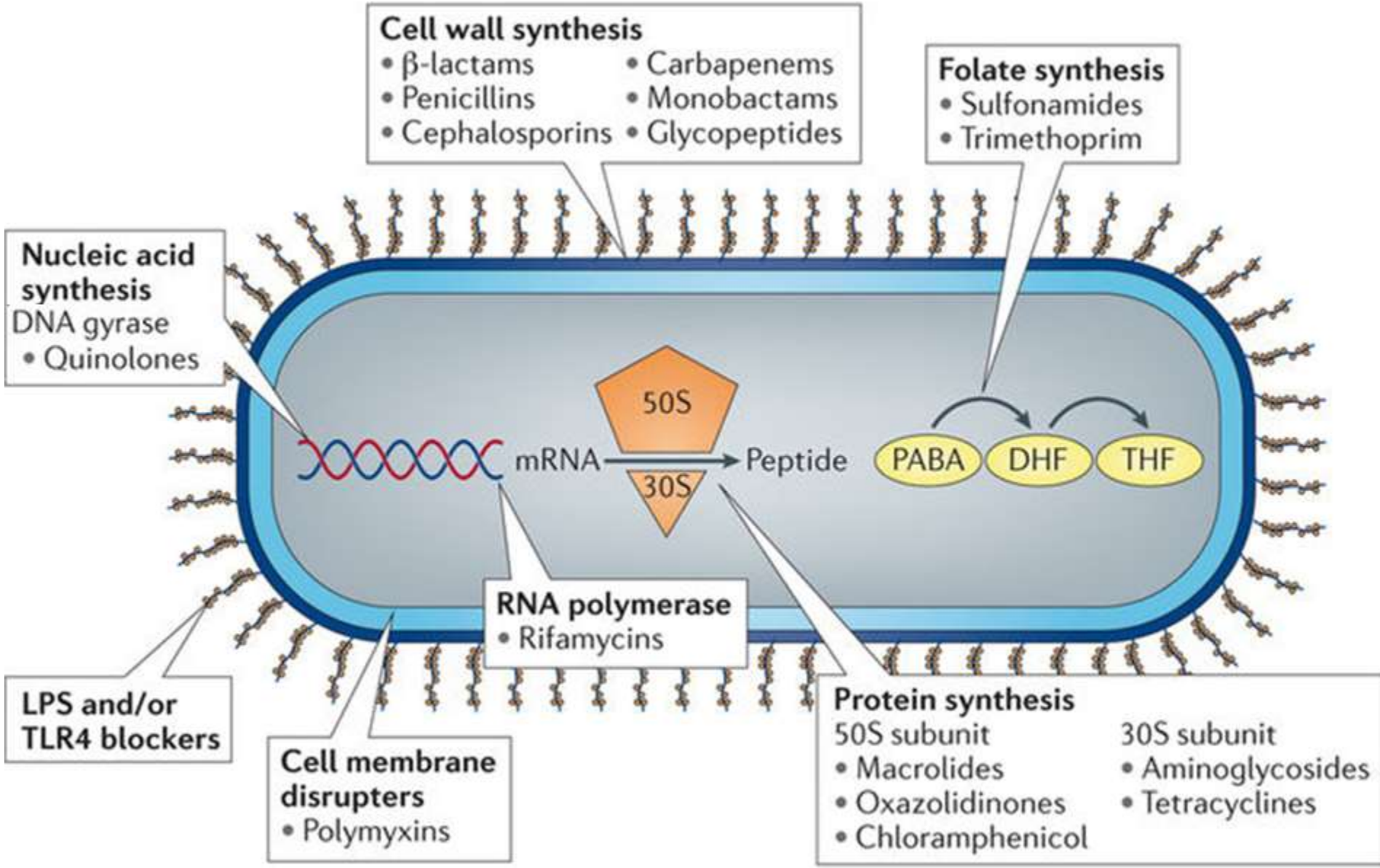
- **Bacteriostatic drugs** arrest the growth and replication of bacteria

- **Bactericidal drugs** kill bacteria

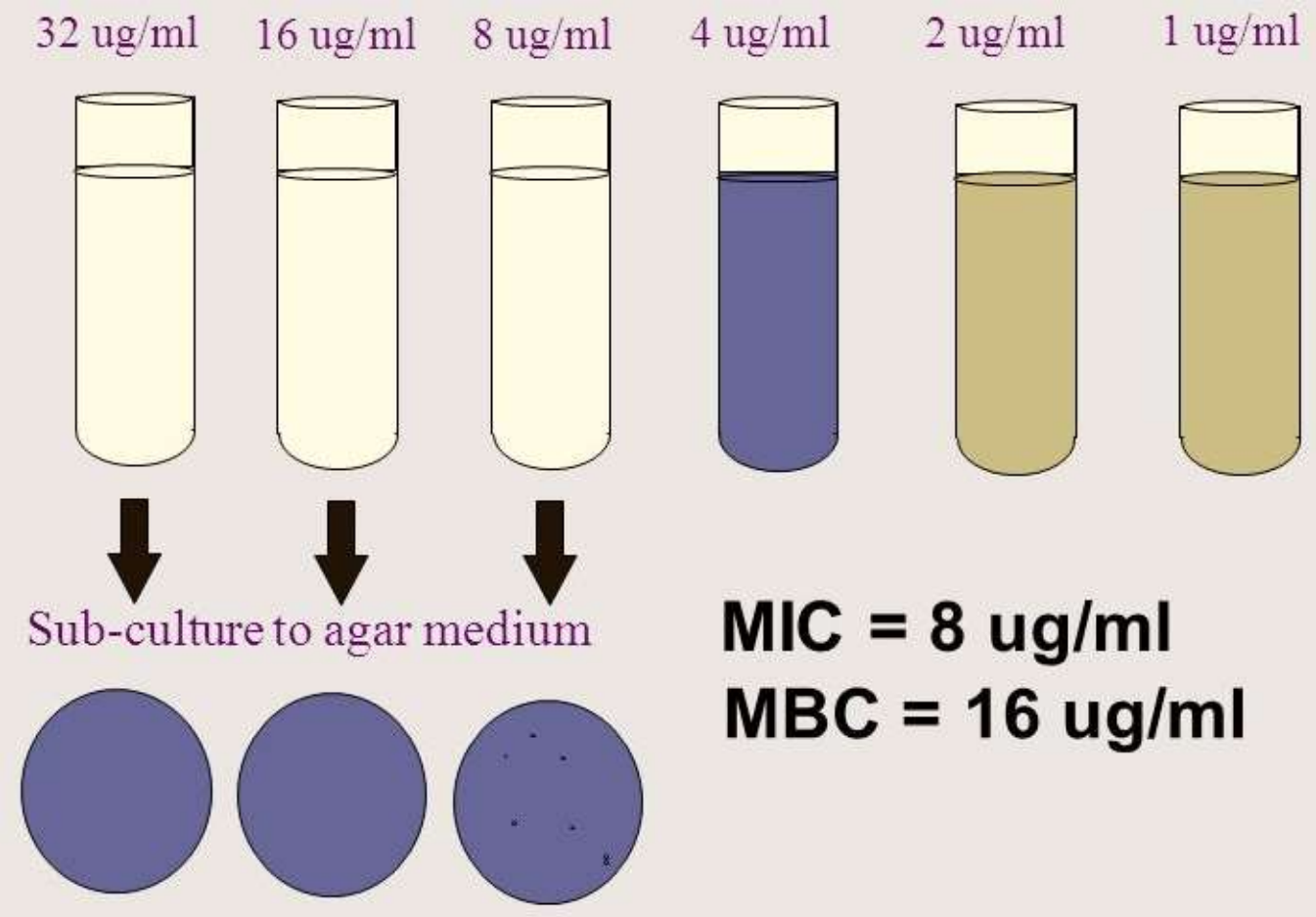
It is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another.

For example, *linezolid* is bacteriostatic against *Staphylococcus aureus* and *enterococci* but is bactericidal against most strains of *S. pneumoniae*.

Mechanisms of Antibacterial Action

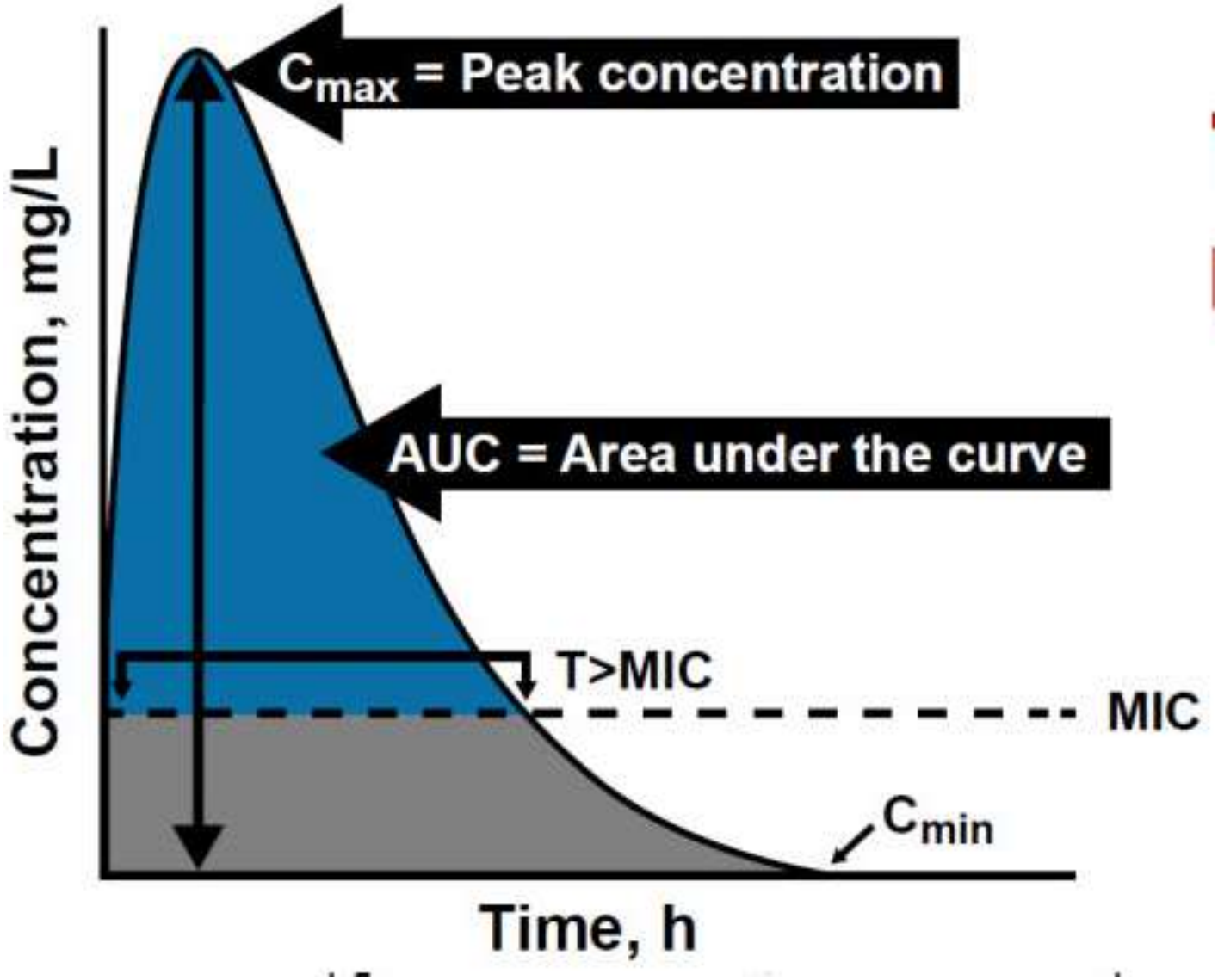


Antibacterial drug activity



- MIC is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation.
- This serves as a quantitative measure of in vitro susceptibility

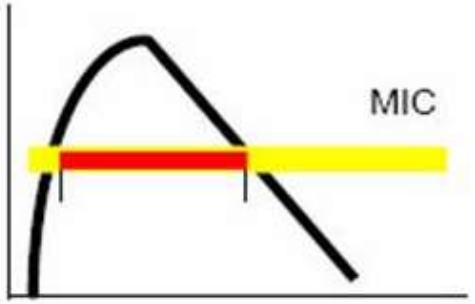
Pharmacodynamic / Pharmacokinetic parameters



Pharmacodynamic / Pharmacokinetic predictors of bacterial eradication

Time >MIC

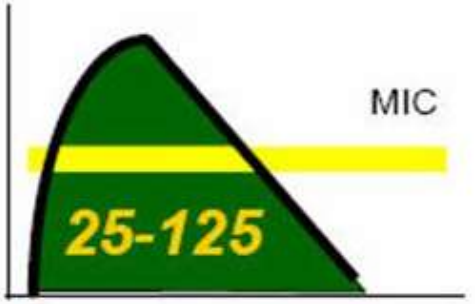
(non-concentration-dependent)



- **Penicillins**
- **Cephalosporins**
- **Erythromycins**
- **Clarithromycin**

AUC_{24}/MIC

concentration-dependent



- **Quinolones**
- **Aminoglycosides**
- **Azithromycin**

25 (gram-positive)
125 (gram-negative)

Craig W. Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. *Clin Infect Dis*. 1998; 26:1-12.

Time dependent antibiotics

The percentage of time that the antibiotic concentration remains above the minimum inhibitory concentration (T>MIC) predicts the efficacy of time-dependent antibiotics

The ideal concentration is 2–4-fold the MIC for at least of 40-60% of the dosing interval. Higher concentration of such drugs does not result in greater killing of organism.

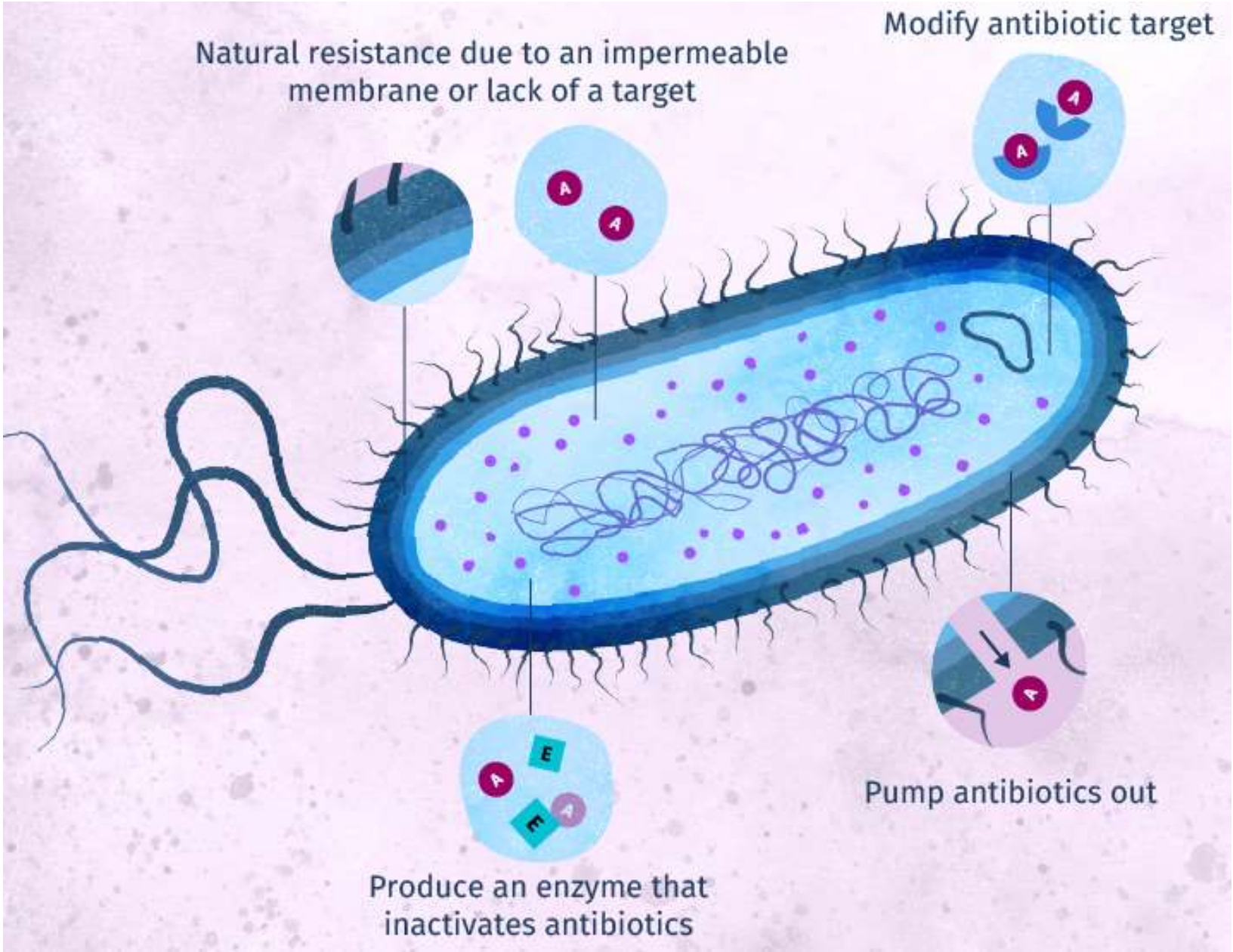
T>MIC can be optimized by increasing antibiotic frequency or using continuous or extended infusions

Examples:
penicillins, cephalosporins, carbapenems, monobactams, clindamycin, macrolides (erythromycin, clarithromycin), oxazolidinones (linezolid).

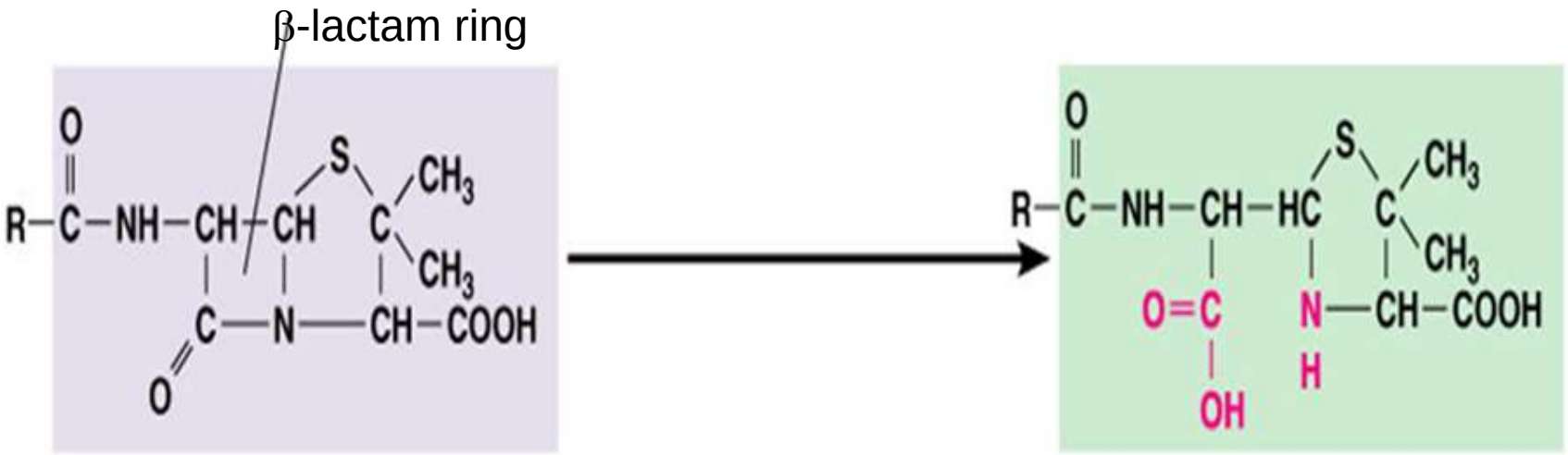
Concentration dependent antibiotics

- Ratio of peak concentration to MIC (Cmax/MIC), and the ratio of the area under the curve to MIC (AUC/MIC) predict the efficacy of concentration-dependent antibiotics
- Cmax is dependent on the dose and is inversely related to Vd, can be optimized by increasing the antibiotic dose.

Mechanism of resistance to antibiotics



Enzymatic inactivation of β-lactams



Thanks for attention!