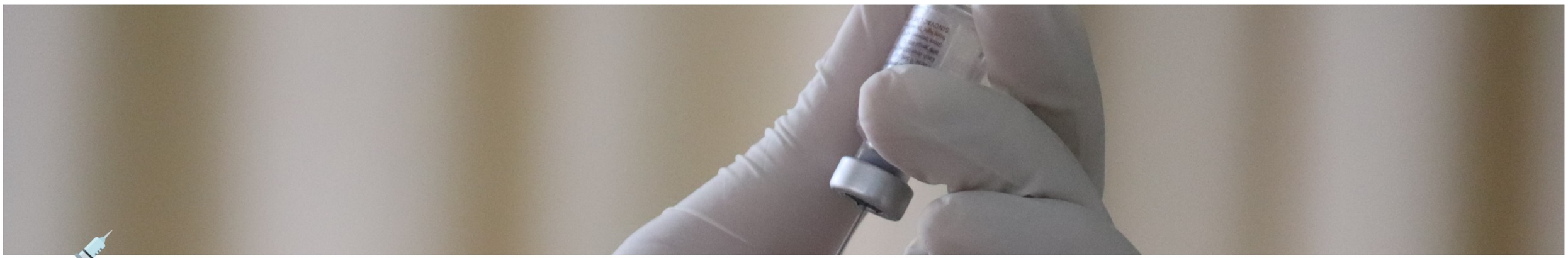

M3 - Antimicrobials & Immunization

3 more properties

Antimicrobial Agent & Antibiotics

Antimicrobial agents (抗微生物药) **kill** and **inhibit** growth of microorganism
- Antibiotics (抗生素) is *a class of antimicrobial.*
- Antibiotics is *produced by a microorganism*

Learning Objective

1.Appreciate the history of antimicrobials development.

Remarks:
- Alexander Fleming discovered that Penicillium kills bacteria in 1928.
- Florey and Chain resurrected Fleming's work in the 40s, isolated penicillin, and by WWII were treating millions with antibiotics.

2.Know different classes of antimicrobials.

3.Understand the basic structure of a bacterium and basic terminologies used in medical microbiology (MIC, MBC, Bactericidal, etc.)

4.Understand the phenomenon of antimicrobial resistance and its consequences.

5.Understand the concept of immunization.

Remarks:
- **Immunization is the process by which an individual's immune system is fortified by natural (e.g. infection) or artificial (e.g. vaccination) means against foreign agents.**

6.Know the types of vaccines and vaccine-preventable diseases.

7.Understand the role of vaccines in reducing burden of diseases and eradication of diseases.

Remarks:
- Vaccination primes the adaptive immune system to the antigens of a particular microbe.
  - **memory T and B cells induce a rapid and effective secondary immune response.**
  - Vaccination depends on **the ability of lymphocytes** to respond to specific antigens and **develop into memory T and B cells**.
- **Vaccination represents a form of actively enhanced adaptive immunity.** (主动增强免疫系统适应能力的方式)
- If a ratio of population are immunized → Inhibit transmission of the infection → **Herd Immunity (群體免疫)**
- ▼ Passive Immunization with Antibodies
  - Before antibiotics, doctors often treated acute infectious diseases by injecting pre-made antibodies. This was based on the idea that the patient was already sick and it was too late for active vaccination.
  - Scientists discovered antibodies in the 1890s by showing that serum from vaccinated rabbits could transfer immunity to tetanus and diphtheria
  - Later on, companies started producing antiserum ("immune serum.") to treat diphtheria, tetanus, pneumococcal pneumonia, and the toxic effects of streptococci and staphylococci.
  - Sometimes, mothers pass antibodies to their babies through the placenta or breast milk. This is a type of natural passive immunity.
  - ▼ Chinese Version

    在使用抗生素治疗急性传染病之前，通常通过注射预先形成的抗体来治疗。这是因为患者已经生病，进行"主动"免疫接种已经太迟了。
    在1890年代，通过用兔子疫苗的血清转移给小鼠，进行了一项关键实验，证明了对破伤风和白喉的免疫力是可以转移的。这是抗体发现的重要实验之一。
    随后，为了治疗白喉、破伤风、肺炎球菌性肺炎以及对链球菌和葡萄球菌的毒性效应，抗血清的生产成为一个重要的产业。
    母体通过胎盘或母乳将抗体传递给婴儿是一种自然发生的被动免疫类型。而被动免疫接种则使用抗体。

▼ Classes of antimicrobials

1. Antibacterial
   - Gram +: Penicillin produced by *penicillium*, a type of bacteria
   - Gram - & Mycobacteria: Streptomycin
     - *Streptomycin* is produced by *Streptomyces griseus*, *where "griseus" means gray and 'Myco-' means 'fungus' in Latin*.
   - Mycobacteria: Isoniazid
     - *Isoniazid* is a *synthetic compound*, which **not a antibiotics**
   - Gram ± & Non-Free living Bacteria:
     - Non-Free living bacteria: Chlamydias & Rickettsias
     - *Tetracycline* is produced by *Streptomyces bacteria*
2. Antiviral
3. Antifungal
   - Ketoconazole (synthetic compound)
4. Antiprotozoal
   - Malaria: Mefloquine (synthetic compound)
5. Antihelmintic
   - Tapeworms: Nidosamide (synthetic compound)
   - Flukes: Praziquantel (synthetic compound)

Do notice that **NOT ALL antibacterial are antibiotics.**
- Isoniazid is not antibiotics but a antibacterial

▼ Examples of Important antiviral agents

Antiviral Agents	Target	Mechanism
Rimantadine/ Amantadine	Influenza A virus (M2 protein)	Target on uncoating of virus by inhibiting viral M2 protein
Tamiflu (oseltamivir), Relenza (Zanamivir)	Influenza virus (A & B) surface protein	Inhibit neuraminidase enzyme, blocking cell-to-cell traffic
Acyclovir, famciclovir	Herpes simplex, Varicella zoster	Inhibit viral DNA polymerase
Ribavirin	Influenza A & B, RSV, Togavirus (e.g. Rubella)	Inhibit viral RNA synthesis
Zidovudine (AZT), Didanosine(ddi), Lamivudine	Retroviruses (HIV)	Act as **Nucleoside RT inhibitors** (NRTI) which inhibit reverse transcriptase enzyme
Nevirapine (Viramune)	HIV	Act as **Non-Nucleoside RT inhibitors (NNRTI)** which bind directly to reverse transcriptase enzyme, inhibiting its activity
Ritonavir, Kaletra	HIV protease	Act as **protease inhibitors (PT)** inhibit protease enzyme, blocking viral maturation
Remdesivir and ritonavir-boosted nirmatrelvir (Paxlovid)	COVID-19	*Remdesivir* is a **nucleoside analogue** that inhibits viral RNA synthesis *Paxlovid* are **PT** that block viral maturation

▼ Introduction to Antibacterial agents

▼ MIC & MBC

- Minimum Inhibitory Concentration (MIC)
  - Smallest concentration of drugs → Bacteriostatic
    - Stops bacterial growth/replication.
  - **Reversible: Stopping Medication will growth.**
  - Sensitivity in vitro
    - Chinese Explanation: 在讨论MIC时，"体外敏感性"是指微生物在实验室环境下被特定抗微生物药物所抑制或杀死的能力，而不是在体内（在活体生物中）的情况。
  - *Bacteriostatic agents: Chloramphenicol*
- Minimum Bactericidal Concentration
  - Smallest concentration → **Irreversibly** (No re-grow) kills microbes
  - *Bactericidal agents: Penicillin*

Inhibitors of Cell Wall Synthesis → Brust due to High Internal Osmotic Pressure

Antibacterial	Mechanism	Susceptibility	Penetration	Origination	Chemical Structure	Effect on Mammalian Cells
Penicillin	peptidoglycan cross-linking.	Natural penicillins are susceptible to penicillinase, which breaks down the penicillin with narrow range of action.	Poor cerebrospinal fluid penetration	Penicillium fungi	β-Lactam ring	No effect Only 2% allergy Only 0.002% Fatal
Cephalosporins	peptidoglycan cross-linking	First gen: better for gram-positive (Staphylococcus, Streptococcus) and gram-negative (E.coli, Klebsiella) Second gen: better for gram-negative (Haemophilus, Gonococcus) and anaerobes Third gen: better for gram-negative rods (Pseudomonas, Providencia) and oral anaerobes Fourth gen: expands antimicrobial spectrum Fifth gen: adds anti-MRSA (methicillin resistant staphylococcus aureus) activity	**3rd and 4th generation** cephalosporins penetrate to CSF	Cephalosporium acremonium.	β-Lactam ring	No effect
Vancomycin	Inhibits synthesis of phospholipids cross-linking of peptidoglycans	Gram-positive organisms b-lactam resistant infections	Widely distributed, penetrates CSF	synthetic compound	Tricyclic glycopeptide	No effect
Teicoplanin	Inhibits synthesis of phospholipids cross-linking of peptidoglycans	Gram-positive organisms b-lactam resistant infections	Widely distributed, penetrates CSF	synthetic compound	Tricyclic glycopeptide	No effect

More about cephalosporins

Generation	Antibacterial
1st	Cephalexin, Cephradine
2nd	Cefuroxime, Cefoxitin
3rd	Cefotaxime, Ceftazidine, Cefixime, Ceftibuten
4th	Cefepime, Cefozopran
5th	Ceftaroline, Ceftobiprole

Inhibitors of Protein Synthesis

The difference between Human Ribosome & Bacterial Ribosome:

Ribosome	Subunits
Human	80S: 40S and 60S
Bacterial	**70S: 30S and 50S**

"S" stands for Svedberg units

- It measures the rate of sedimentation during centrifugation
- It is a unit of time used to measure the breakdown of particles into smaller units

Medically Important Examples of Protein Synthesis Inhibitors

Antibacterial	Examples	Original	Pros	Cons	Reversibility	Subunit
Tetracyclins	Demeclocycline Doxycycline Minocycline Tetracycline	Isolated from Streptomyces	sinus mucosa saliva tears	Poor gut absorption	Reversible	30S subunit
Aminoglycoside	Amikacin Gentamicin Streptomycin Tobramycin	Derived from Streptomyces and Micromonospora	Actively transported into bacterial cells	Poor gut absorption	Irreversible	30S subunit
Macrolides	Azithromycin Clarithromycin Erythromycin	Macrocyclic lactone structure	Therapeutic concentrations in oropharyngeal and respiratory secretions	No CSF penetration	Reversible	50S subunit
Chloramphenicol	Chloramphenicol	Isolated from Streptomyces	Broad spectrum of activity widely distributed enters CSF	Indicated for severe anaerobic infections or unresponsive life-threatening infections	Reversible	50S subunit
Clindamycin	Clindamycin	Semisynthetic derivative of Lincomycin	anaerobes Gram positive aerobes head and neck infections	Penetrates saliva, sputum, and bone, but not CSF	Reversible	50S subunit

Remarks: If an antibacterial agent is **reversibly bond** to subunit of ribosome, it will **also inhibits** some of the protein synthesis process by *forming **weak bonding** to the subunit of ribosomes*.

Inhibitors of Nucleic Acid (DNA Replication / RNA Synthesis)

Antibacterial	DNA/RNA	Mechanism	Concentration in body	Penetration	Origination
Fluoroquinolones	DNA Replication	Bind bacteria DNA gyrase (topoisomerase II)	sinus and middle ear mucosa	penetrate cartilage and bone	Synthetic compound
Rifamycins	mRNA Synthesis	Bind to DNA-dependent RNA polymerase	saliva,	cross the blood-brain barrier	Natural compound

Inhibitors of Metabolism

Antibacterial	Enzyme Inhibited	Mechanism
Sulfonamides	Dihydropteroate synthase	Inhibit production of folic acid coenzymes
Trimethoprim	Dihydrofolate reductase	Inhibit production of folic acid coenzymes

Folic acid coenzymes is required for **purine and pyrimidine synthesis**

- Essential for bacterial DNA synthesis

Antimicrobial Resistance

Antibacterial Agents	Methicillin Resistant Staphylococcus aureus (MRSA)	Extended-Spectrum β-Lactamases (ESBL)	Penicillin Resistant S. pneumoniae (PRSP)	Multi-Resistant S. pneumoniae (MRSP)	Vancomycin Intermediate Resistant S. aureus (VISA)	Vancomycin Resistant S. aureus (VRSA)
Most β-lactams	✗ (Only anti-MRSA cephalosporins)	✗ (Only Carbapenems)	✗	✗	✓	✓
Vancomycin	✓	✓	✓	Nil	✗	✗
Linezolid (New Vancomycin)	✓	✓	✓	Nil	✗	✗

ESBL (*Extended-Spectrum β-Lactamases*) can be found in:
- Klebsiella Pneumoniae
- Escherichia Coli
- Salmonella

Two types of Antimicrobial Resistance

- Intrinsically resistant (先天性抗药性):
  - Impermeable to the drug
  - Lack of target binding site
  - Production of enzymes that can destroy antibiotics
- Acquired resistance (genetic modification):
  - Mutations that alter permeability to the antibiotic
  - Mutations that alter the target site
  - [1]Switch on a gene of an enzyme that can destroy the antibiotic
  - [2]Acquiring a gene (e.g., on a plasmid), the product of which can destroy the antibiotic

Remarks:
- 1st statement: **a change within** the organism's **own genetic material**
- 2nd statement: **the acquisition** of genetic material **from outside the organism**.

Types of Vaccine

Types of vaccine	Classification	Examples	Characteristics
Viral	`Live attenuated`	Measles, mumps, rubella, vaccinia, varicella, yellow fever, zoster, oral polio, intranasal influenza, rotavirus	Weakened version of the virus that still replicates in the body to stimulate an immune response
Bacterial	`Live attenuated`	BCG, oral typhoid	Weakened version of the bacteria that still replicates in the body to stimulate an immune response
Whole virus	`Inactivated`	Polio, influenza, hepatitis A, rabies	Virus is killed or inactivated so it cannot replicate in the body, but still stimulates an immune response
Whole bacteria	`Inactivated`	Pertussis, cholera, typhoid	Bacteria is killed or inactivated so it cannot replicate in the body, but still stimulates an immune response
Toxoids	`Fractions`	Diphtheria, tetanus	Inactivated toxins produced by the bacteria
Protein subunits	`Fractions`	Hepatitis B, influenza, acellular pertussis, human papillomavirus	Pieces of the virus or bacteria that stimulate an immune response
Polysaccharides	`Fraction=s`	Pneumococcal, meningococcal, Salmonella typhi (Vi), Haemophilus influenzae B	Carbohydrates from the outer surface of the bacteria that stimulate an immune response
Conjugates	`Fractions`	Haemophilus influenzae B, pneumococcal, meningococcal	Polysaccharides from the bacteria are linked to a protein to enhance the immune response

Safety of Vaccine

Live attenuated vaccines

- Not weakened enough
- Reverting back to the dangerous form of the virus
- Given to someone with a weak immune system
- Virus that stays in the body too long
- Infected by other viruses
- Harmful to a developing fetus

Non-living vaccines

- Contaminated with harmful chemicals or toxins
- Allergic reactions
- Can cause autoimmunity

Genetically engineered vaccines

- May contain cancer-causing genes

活体减毒疫苗

- 没有被削弱到足够程度
- 变回病毒的危险形态
- 给免疫系统较弱的人接种
- 病毒在体内停留的时间过长
- 被其他病毒感染
- 对发育中的胎儿有害

非活体疫苗

- 被有害化学物质或毒素污染
- 过敏反应
- 可能导致自身免疫病

基因工程疫苗

- 可能含有致癌基因