Multidrug therapy

- To kill all bacteria, and to prevent resistance

one drug help the other

- Example:

Mycobacterium tuberculosis:

(isoniazid + rifampin + pyrazinamide + ethambutol)

if we use one drug bacteria can develope resistance
using multidrugs will delay resistance development which is a benefit of multidrug therapy

Synergism

Degree of killing that is far greater than that achieved by either drug alone or the sum of both

Example: Co-trimoxazole (Trimethoprim **+** sulfamethoxazole)

1+1>2
powerfull effect

Antagonism

Degree of killing that is less than that achieved by either drug alone

Example: Penicillin + Tetracycline (**WHY ?**)

because penicillin needs an actively dividing cell to work in its cell wall
while tetracycline inhibite protein synthesis
bactericidal "penicillin " won't work with a bacteriostatic "tetracycline"

Antifungal Agents

- Toxic to patients (**WHY?**)

many side effects are observed when antifungal are used to treat a systemic infection

- **Mechanism of action**:

1. Binding cell membrane sterol

   e.g. Nystatin, Amphotericin-B

2. Interfere with sterol synthesis

   e.g. Clotrimazole, miconazole

3. Blocking mitosis, or nucleic acid synthesis

   e.g. Griseofulvin, 5-flucytosine

you must be aware about the difference between coltimazole "antifungal" and cotrimoxazole "anti bacterial"

miconazole used for the moouth infection "C

Mycoheal gel mouth and tungue

Antiprotozoal Agents

- Toxic to human cells (**WHY?**)

because there is no selective toxicity and they act on human cells so they are harmfull
"selective toxicity is found in antibacterial"

- Mechanism of action

1. Interfere with DNA and RNA synthesis

   e.g. Chloroquine, pentamidine, quinacrine

very commonly available in infection

Chloroquine is antimalaria drug and other can be use for malaria

2. Interfere with protozoal metabolism

   e.g. Metronidazole (Flagyl)

dentists use them in anaerobic bacteria

Antiviral Agents

- Relatively few agents are available

used against HIV

not many antiviral are available

- **WHY?** - see your textbook

- Examples:
  - Anti-HIV: Zidovudine (AZT); 1989

Table 9-3 Antifungal Agents

Drug[a]	Fungal Disease(s) That the Drug Is Used to Treat
Amphotericin B	Aspergillosis, blastomycosis, invasive candidiasis, coccidioidomycosis, cryptococcosis, fusariosis, histoplasmosis, mucormycosis, paracoccidioidomycosis, penicilliosis, systemic sporotrichosis
Atovaquone	*Pneumocystis* pneumonia
Echinocandins	Aspergillosis, candidiasis
Fluconazole	Blastomycosis; oropharyngeal, esophageal, and invasive candidiasis; coccidioidomycosis, cryptococcosis, fusariosis, histoplasmosis, sporotrichosis
Flucytosine	Candidiasis, chromoblastomycosis, cryptococcosis
Griseofulvin	Dermatomycosis (less toxic drugs are available, however)
Itraconazole	Aspergillosis, blastomycosis, invasive candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, penicilliosis, pseudallescheriasis, scedosporiosis, cutaneous or systemic sporotrichosis
Ketoconazole	Blastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis
Terbinafine	Dermatomycosis
Trimethoprim-	*Pneumocystis* pneumonia sulfamethoxazole
Voriconazole	Aspergillosis, invasive candidiasis, scedosporiasis

مش حفظ

Table 9-4 Antiprotozoal Agents

Drug[a]	Protozoal Disease(s) That the Drug Is Used to Treat
Amphotericin B	Primary amebic meningoencephalitis, mucocutaneous leishmaniasis
Artemisinin derivatives	Multidrug-resistant *Plasmodium falciparum* malaria
Benznidazole	American trypanosomiasis (Chagas disease)
Chloroquine phosphate or quinidine gluconate or quinine dihydrochloride	Malaria (except for chloroquine-resistant *P. falciparum* malaria and chloroquine-resistant *Plasmodium vivax* malaria)
Clindamycin plus quinine	Babesiosis
Diloxanide furoate	Amebiasis
Eflornithine	African trypanosomiasis (with or without CNS involvement)
Furazolidone	Giardiasis
Halofantrine	Chloroquine-resistant *P. falciparum* malaria
Iodoquinol	Amebiasis, balantidiasis, *Dientamoeba fragilis* infection
Mefloquine	Chloroquine-resistant *P. falciparum* and *P. vivax* malaria
Melarsoprol	African trypanosomiasis (with CNS involvement)
Metronidazole	Amebiasis, giardiasis, trichomoniasis
Nifurtimox	American trypanosomiasis (Chagas disease)
Nitazoxanide	Giardiasis in children and cryptosporidiosis
Paromomycin	Amebiasis, cryptosporidiosis, *D. fragilis* infection, cutaneous leishmaniasis
Pentamidine isethionate	African sleeping sickness (without CNS involvement), leishmaniasis
Primaquine phosphate	Malaria
Proguanil hydrochloride	Malaria
Pyrimethamine plus sulfadiazine	*P. falciparum* malaria, toxoplasmosis

مش حفظ

Table 9-4 Antiprotozoal Agents (*Continued*)

Drug[a]	Protozoal Disease(s) That the Drug Is Used to Treat
Quinacrine hydrochloride	Giardiasis
Quinidine gluconate	*P. falciparum* malaria
Quinine	Malaria
Spiramycin	Toxoplasmosis
Stibogluconate sodium	Visceral, cutaneous, and mucocutaneous leishmaniasis
Suramin	African trypanosomiasis (with no CNS involvement)
Tetracycline hydrochloride	Balantidiasis, *D. fragilis* infection; can be used with quinine or quinidine for *P. falciparum* malaria
Tinidazole	Amebiasis, giardiasis, trichomoniasis
Trimethoprim–sulfamethoxazole	Cyclosporiasis, isosporiasis

مش حفظ

Table 9-5 Antiviral Agents

Virus/Viral Infection(S)	Antiviral Agents[a]
Herpes simplex infections	Acyclovir, cidofovir, famciclovir, fomivirsen, foscarnet, ganciclovir, penciclovir, valacyclovir, valganciclovir, vidarabine
Influenza virus types A and B	Oseltamivir, ribavirin, zanamivir
Hepatitis B virus	Adefovir, entecavir, peginterferon α-2a, lamivudine, telbivudine, tenofovir
Hepatitis C virus	Peginterferon α-2a, ribavirin
Human cytomegalovirus	Cidofovir, foscarnet, ganciclovir
Varicella-zoster virus	Acyclovir, famciclovir, valacyclovir
HIV: nucleoside/-tide analog reverse transcriptase inhibitors	Abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine (AZT, ZDV)
HIV: non-nucleoside reverse transcriptase inhibitors	Delavirdine, efavirenz, etravirine, nevirapine
HIV: protease inhibitors	Amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir
HIV: fusion inhibitor	Enfuvirtide
HIV: integrase inhibitor	Raltegravir

مش حفظ
ما عدا اول واحد

Drug resistance

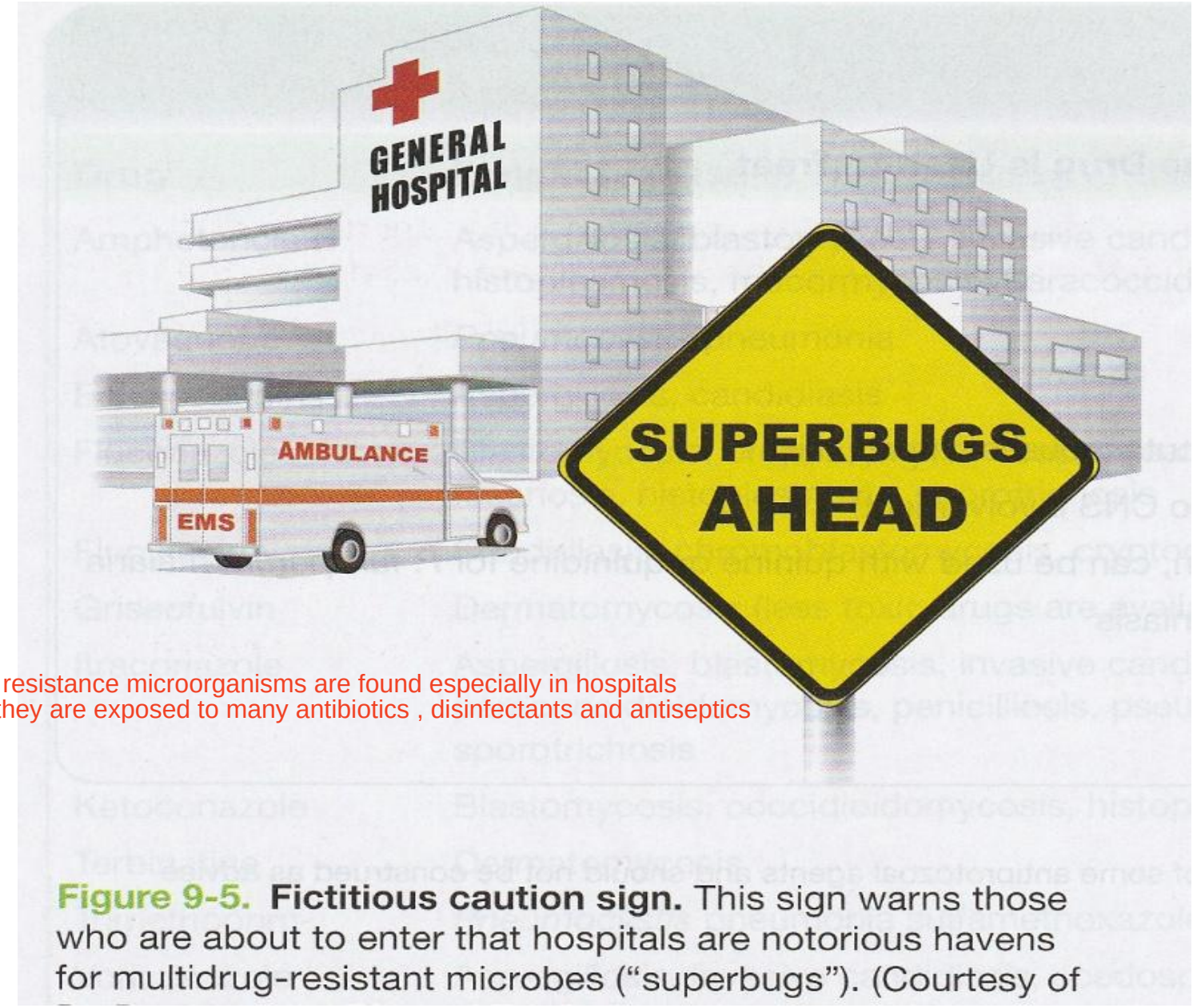
- Drug resistant bacteria (Superbugs)

  microbes protect themselves by many mechanisms
  to develop resistance against antimicrobial

- Superbugs USUALLY Multidrug Resistant

- Viruses/HIV, Fungi, Protozoa, Helminthes
  (Also, Multidrug Resistant)

- See the Table



multidrug resistance microorganisms are found especially in hospitals
because they are exposed to many antibiotics , disinfectants and antiseptics

Figure 9-5. Fictitious caution sign. This sign warns those who are about to enter that hospitals are notorious havens for multidrug-resistant microbes ("superbugs"). (Courtesy of

Table 9-6 Especially Troublesome "Superbugs"

مهم جدا الشرح تحت الجدول

Bacteria	Discussion
MRSA and MRSE (Fig. 9-6)	These strains are resistant to all antistaphylococcal drugs except vancomycin and several recently developed drugs (e.g., linezolid, tigecycline, quinupristin-dalfopristin, daptomycin, ceftaroline). Some strains of *S. aureus*, called vancomycin-intermediate *S. aureus* (VISA), have developed resistance to the usual dosages of vancomycin, necessitating the use of higher doses to treat infections caused by these organisms. Recently, strains of *S. aureus* (called vancomycin-resistant *S. aureus* or VRSA strains) have been isolated that are resistant to even the highest practical doses of vancomycin. *S. aureus* is a very common cause of healthcare-associated infections[a] (Fig. 9-6). *S. epidermidis* is not as virulent or versatile as *S. aureus*, but this organism does cause many hospital-associated infections (especially urinary tract infections and infections associated with foreign objects, such as intravenous catheters, prosthetic heart valves, and prosthetic joints). Most strains of *S. epidermidis* are resistant to penicillin, and many strains are resistant to the antistaphylococcal penicillins.
Streptococcus pyogenes and *Streptococcus pneumoniae*	*S. pyogenes* and *S. pneumoniae* are very important human pathogens, in that they cause a wide variety of infectious diseases. Strains of *S. pyogenes* that are resistant to macrolide antibiotics have emerged, but fortunately, all strains of *S. pyogenes* remain susceptible to penicillin. The same is not true for *S. pneumoniae*. Many strains of *S. pneumoniae* have developed resistance to penicillin and other beta-lactam antibiotics.
Vancomycin-resistant *Enterococcus* spp. (VRE)	These strains are resistant to most antienterococcal drugs, including vancomycin. *Enterococcus* spp. are common causes of healthcare-associated infections, especially urinary tract infections.
P. aeruginosa	*P. aeruginosa* infections are very common and especially difficult to treat. Strains of *P. aeruginosa* have a variety of resistance mechanisms, including a relatively impermeable outer membrane and multiple efflux pumps. Aminopenicillins, macrolides, and most cephalosporins are ineffective against *P. aeruginosa*.
Clostridium difficile	*C. difficile* is a major cause of hospital-associated diarrheal disease. Strains of *C. difficile* have become resistant to clindamycin, ciprofloxacin, and levofloxacin.

الدكتور أكد على أهمية الجدول 🤷‍♀️

Urinary infection

Like cephalosporins

It is a pathogenic

MRSE =methicillin-resistant staphylococcus epidermidis
resistance to penicillin and cyphalosporins

MRSA= methicillin-resistant staphylococcus aureus

*they develpe resistance
against many drugs
but they are sensitive to
vancomycin.
*vancomycin is the drug of choice
for MRSA
*MRSE not agressive as MRSA
its important in UTI

*VISA : we can overcome its
action by increasing vancomycin
dose " intermediate resistance
to vancomycin

*VIRSA completly resistance so we use daptomycinor linezolid"

streptogriamn = daptomycin+ lenezolid
works against VRSA

What's your alternative to vancomycin?
Daptomycin or lenzezolid or streptogriamn

*streptoccocus pyogenes and streptoccous pneumonia

s.pyogenes :
cause sore throat , tonsilities
sensitive to penicillin so penicillin is a good choice for treatmeant
some people are allergic to penicilln
so they use erthromycin buts.pyogenes srarts developing resistance against it

s.pneumonia:
cause pneumonia and other infections
resistance to penicillin and many b lactam

Table 9-6 Especially Troublesome "Superbugs" (*Continued*)

Bacteria	Discussion
Acinetobacter baumannii	Infections caused by multidrug-resistant strains of *A. baumannii* were first reported in military personnel stationed in Iraq and Afghanistan. Some strains were resistant to all drugs tested.
Klebsiella pneumoniae	Carbapenemase-producing strains of *K. pneumoniae* produce a β-lactamase that destroys penicillins, cephalosporins, aztreonam, carbapenemes, and other antibiotics.
Multidrug-resistant *M. tuberculosis* (MDR-TB)	MDR-TB strains are resistant to the two most effective first-line therapeutic drugs—isoniazid and rifampin. Extensively drug-resistant strains, called XDR-TB, are also resistant to the most effective second-line therapeutic drugs—fluoroquinolones and at least one of the following: amikacin, kanamycin, capreomycin. Some drug-resistant strains of *M. tuberculosis* are resistant to *all* antitubercular drugs and combinations of these drugs. Patients infected with these strains may require removal of a lung or section of a lung—just as in the preantibiotic days—and many will die. Tuberculosis remains one of the major killers worldwide.
Multidrug-resistant strains of *Burkholderia cepacia*, *E. coli*, *Neisseria gonorrhoeae*, *Ralstonia pickettii*, *Salmonella* spp., *Shigella* spp., *Stenotrophomonas maltophilia*, and *H. influenzae*	ازالة الرئه كانت احدى العلاجات المتبعه قديما قبل اكتشاف ال antibiotics

rare microbes
multidrug resistance

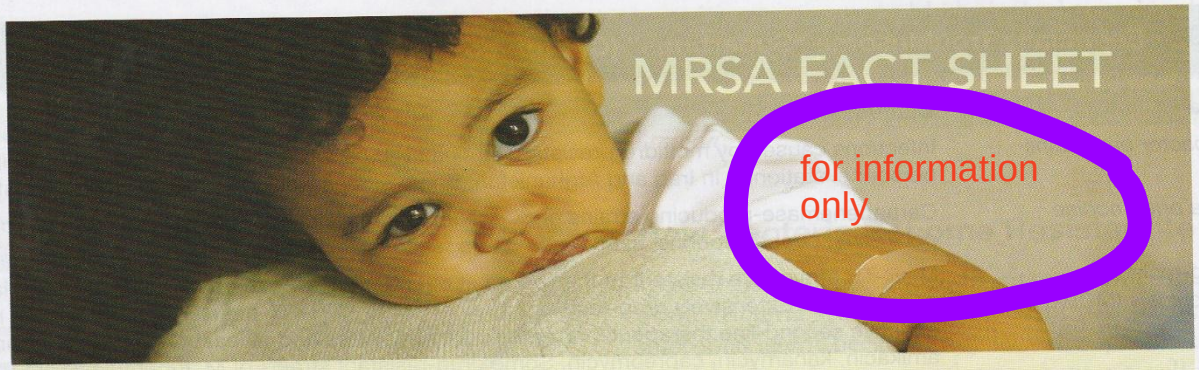
drug used for TB= rifampin + linezoild
many drugs are used to reduce resistance
ولكن ظهرت سلالات جديده
لا تستطيع هذه الادويه علاجها

Make pneumonia and multiple infection

Important Resistant Bacteria

- MRSA, MRSE
- VISA, VRSA;
- VRE (UTI)
- *P. aeruginosa*
- *Clostridium difficile*
- *Acinetobacter baumanni*
- *Klebsiella pneumonia*
- *M. tuberculosis* (MDR-TB)

What to do?



MRSA FACT SHEET

for information only

What is MRSA?

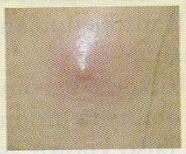
MRSA is methicillin-resistant *Staphylococcus aureus*, a potentially dangerous type of staph bacteria that is resistant to certain antibiotics and may cause skin and other infections. As with all regular staph infections, recognizing the signs and receiving treatment for MRSA skin infections in the early stages reduces the chances of the infection becoming severe. MRSA is spread by:

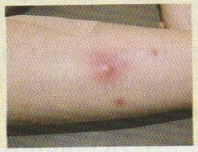
- Having direct contact with another person's infection
- Sharing personal items, such as towels or razors, that have touched infected skin
- Touching surfaces or items, such as used bandages, contaminated with MRSA

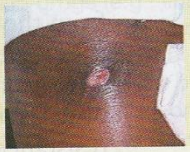
What are the signs and symptoms?

Most staph skin infections, including MRSA, appear as a bump or infected area on the skin that may be:

- Red
- Swollen
- Painful
- Warm to the touch
- Full of pus or other drainage
- Accompanied by a fever







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http://phil.cdc.gov

What if I suspect an MRSA skin infection?

Cover the area with a bandage and contact your healthcare professional. It is especially important to contact your healthcare professional if signs and symptoms of an MRSA skin infection are accompanied by a fever.

How are MRSA skin infections treated?

Treatment for MRSA skin infections may include having a healthcare professional drain the infection and, in some cases, prescribe an antibiotic. Do not attempt to drain the infection yourself – doing so could worsen or spread it to others. If you are given an antibiotic, be sure to take all of the doses (even if the infection is getting better), unless your healthcare professional tells you to stop taking it.

How can I protect my family from MRSA skin infections?

- Know the signs of MRSA skin infections and get treated early
- Keep cuts and scrapes clean and covered
- Encourage good hygiene such as cleaning hands regularly
- Discourage sharing of personal items such as towels and razors

For more information, please call 1-800-CDC-INFO or visit www.cdc.gov/MRSA.

Mechanisms of bacterial resistance

- Lack specific target, e.g. *M. pneumoniae* (no cell wall)

مهم نعرف انه ال Penicillin ما بأثر فيها لأنه ما عندها cell wall

عليها سؤال بالامتحان

- Intrinsic resistance: Natural

streptoccocus is naturally resistance to aminoglycosides like gentamycin and amikacin

- Acquired resistance: Changed/Acquired

- FOUR mechanisms (See the Table)

drug have to bind with the target to make an action
important Q:
can we use penicillin to kill M.tuberculosis?
no because penicillin acts on the peptidoglyc
found in the cell wall and this type of microbe has no cell wall

- Resistance Factor (**R- Factor**); **Conjugation**

- **MDR Pumps (Transporter/ Efflux Pump)**

multi drug resistance pump
البكتيريا بتطلع الدوا وبتمنع انه يتركز جوا وبالتالي بتمنع تأثيره

معناها باتجاه الخارج

IMPORTANT

Table 9-7 Mechanisms by Which Bacteria Become Resistant to Antimicrobial Agents

Mechanism	Effect
A chromosomal mutation that causes a change in the structure of a drug-binding site	The drug cannot bind to the bacterial cell
A chromosomal mutation that causes a change in cell membrane permeability	The drug cannot pass through the cell membrane and thus cannot enter the cell
Acquisition (by conjugation, transduction, or transformation) of a gene that enables the bacterium to produce an enzyme that destroys or inactivates the drug	The drug is destroyed or inactivated by the enzyme B lactamase , penicillinase
Acquisition (by conjugation, transduction, or transformation) of a gene that enables the bacterium to produce an MDR pump	The drug is pumped out of the cell before it can damage or kill the cell Help in drug expulsion

Beta-Lactamases

- Beta-lactam antibiotics with Beta-lactam ring are affected with these enzymes.
- Two types:
    1. Penicillinases
    2. Cephalosporinases

- Some bacteria produce one or both enzymes

Prevention of Beta-lactamase action

Combine antibiotics with Inhibitors:

Examples:

some drugs are B lactamase resistance
such as nafcillin , others need a shiled to protect them

Clavulanic acid + Amoxicillin = Augmentin

provide protection to B lactam ring

الأسماء التجارية فقط للمعرفة

Clavulanic Acid + Ticarcillin = Timentin

Sulbactam + Ampicillin = Unasyn

Tazobactam + Piperacillin = Zosyn

act mainly in GI

piperacillin =new generation of penecillins acts mainly on G-ve
"antipseudomonal"

Strategies against drug resistance

- Education, Prudent use

here is a fight between microbes and scientists
humans are losing because of misuse of antibiotics
so we have to use antibiotics prudently in order to win the battle
prudnat = الاستعمال الرشيد

- Proper prescription (**most unnecessary**)

مثل وصف بعض الأطباء المضادات الحيوية لل flu ولكن انا هون
antiviral بحتاج ال

- First: Narrow spectrum & inexpensive

وصف الادوية الباعظة للمريض مع وجود بديل أرخص
malepractise =

- Complete the full coarse as prescribed

and decrease antimicrobial agent

- No need for prophylactic unless by clinician
- Good infection control and prevention

antiseptics, disinfectants,sterilization= decrease probability of infection

Table 9-8 Viral Infections for Which Antibiotic Treatment Is Deemed Inappropriate

Infection	Usually Caused by Viruses	Usually Caused by Bacteria	Antibiotic Needed
Cold	Yes	No	No
Flu	Yes	No	No
Chest cold (in otherwise healthy children and adults)	Yes	No	No
Sore throats (other than strep throat)	Yes	No	No
Bronchitis (in otherwise healthy children and adults)	Yes	No	No
Runny nose (with green or yellow mucus)	Yes	No	No
Fluid in the middle ear	Yes	No	No

if we use antibiotics in these cases it will worsen the condition because the normal flora will be killed which provides more space for harmful bacteria >> increase it's growth >> antimicrobial resistance

Empiric therapy

To " guess"; "educated guess":

- Pocket chart/Antibiogram (Clinical Microbiology Lab)
- Allergy history of the patient some have allergy to penicillin could be lethal
- Age we can't use some drugs for children or old people
- Pregnancy
- Inpatients can't be given out the hospital
- Site of infection, e.g. Brain, bladder, etc.?
- Drug cross-reaction certain drugs are harmful
  patients using antilipid drygs can't take some types of antimicrobial drugs
- Toxic side effects
- Immune status immunocompromised or immunocomptent قوي المناعة وضعيف المناعة
- Cost it's important to be effective rather than being expensive

Undesirable effects of antimicrobial agents

- Selecting for drug-resistant organisms
- Allergy

when some microbes are killed and others still viable and can cause disease at the end this leads to develop resistance against antibiotics

- Toxic, e.g. Chloramphenicol ➡ Aplastic Anemia

  Streptomycin ➡ Deafness

allergy: *chlorophenicol cause many side effects now it's used rarely and stopped in many hospitals. *sterptomycin combined with gentamycin used to treart diarreah in childrens could cause deafness.

- Superinfection "**population explosion**", Fig.
  - By opportunistic or secondary invaders

unnecessary use

  - Example: *C. difficile* ➡ antibiotic-associated/ pseudomembranous colitis, e.g. Lincomycin
  - *Candida albicans* ➡ Vaginitis; e.g. Tetracycline

using tetracyclin for a long time will lead tp overgrowth of some yeasts " candida albicans" while inhibiting important bacteria >> vaginitis

لما نستخدم مضادات حيوية اللي باللون الأحمر راح تموت واللي باللون الأخضر راح تتكاثر وتسبب المرض
الأحمر يعني sensitve
والأخضر resistance

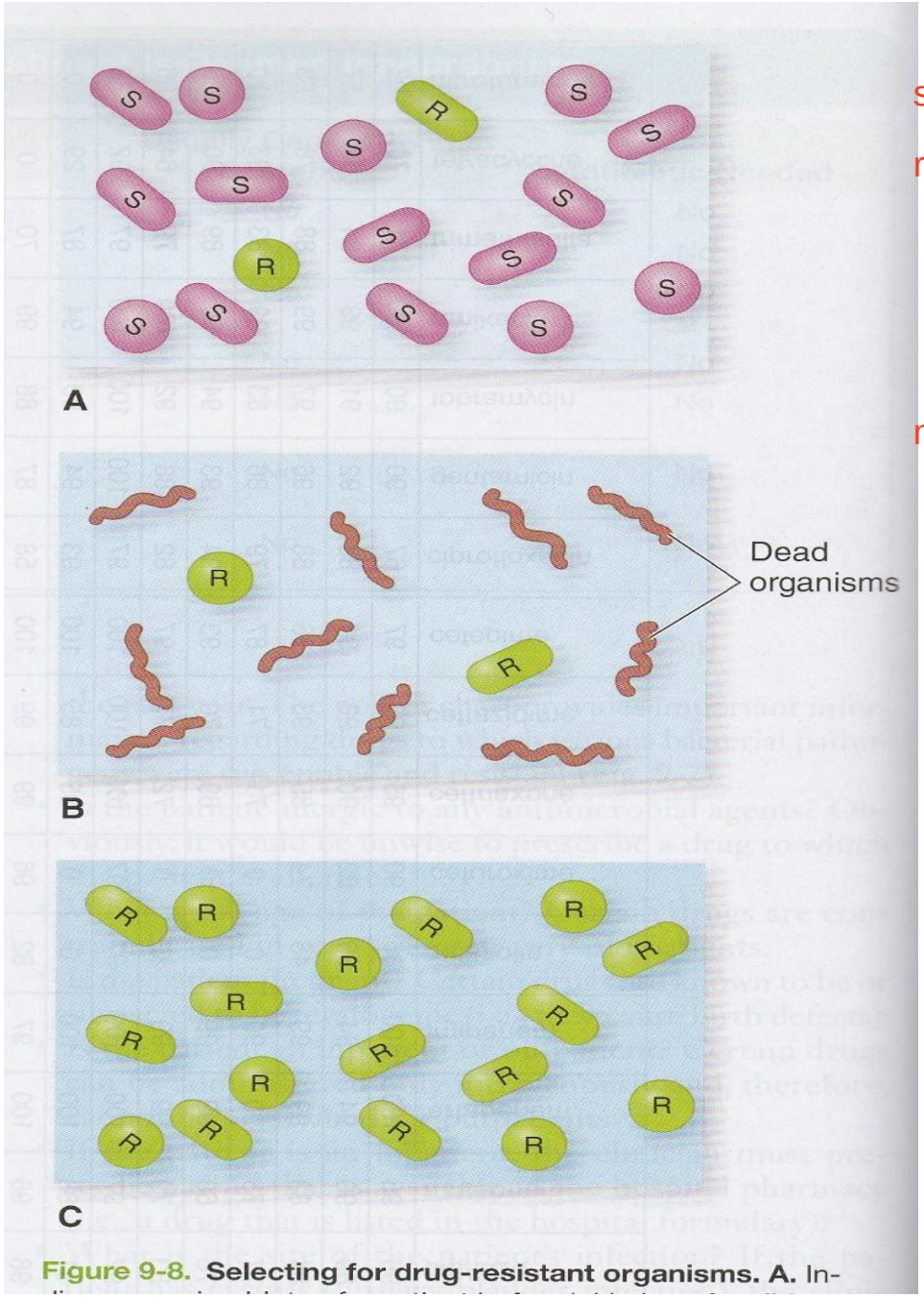


Figure 9-8. Selecting for drug-resistant organisms. A. In-

sesitive bacteria will be killed

resistance bacteria won't be k

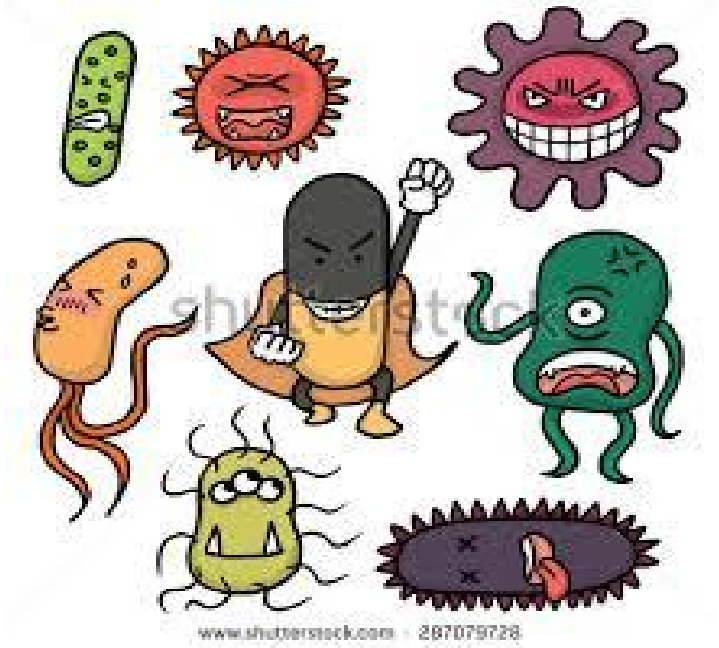
Killed

more space for resisitance ba

bacteria

resistance bacteria will multibly and cause diseas
e.g pseudomembranous c

Callitise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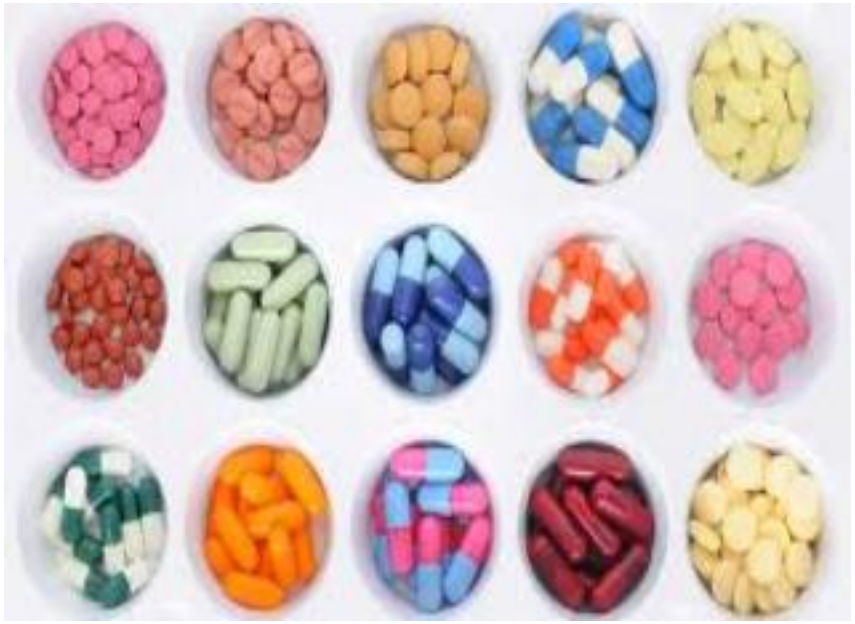


I think I need antibiotics for my col...
IT'S A VIRUS!


BACTERIA VS. ANTIBIOTICS