18. Tuberculosis- part 9

Treatment of tuberculosis- regimens

This is the last part of the topic.

18.1. Some basic principles

18.1.1.What are the different types of drug therapy?

Basic types of treatment with drugs are prophylactic, etiotropic, pathogenic, and symptomatic. *Prophylactic* drug is an agent that acts to prevent a disease, e.g., covid or BCG vaccine to prevent covid 19 and Tuberculosis disease. *Etiotropic* therapy is directed against the cause; etiotropic agent reduces or destroys the causal factor of a disease, e.g., antibiotic drugs. *Pathogenic* therapy is directed on the pathologic, physiologic, or

biochemical mechanism resulting in the development of a disease process, e.g., uses of digoxin during *heart insufficiency (pathogenic process).* Finally, *symptomatic* therapy is directed on removing of symptoms of a disease (painkillers which reduce or remove pain).

Antibiotic can be used as a *prophylaxis* to prevent

symptomatic manifestation of disease (INH prophylaxis in Latent tuberculosis infection) or to *treat symptomatic infectious disease* (INH in combination with other antibiotics for treating tuberculous disease).

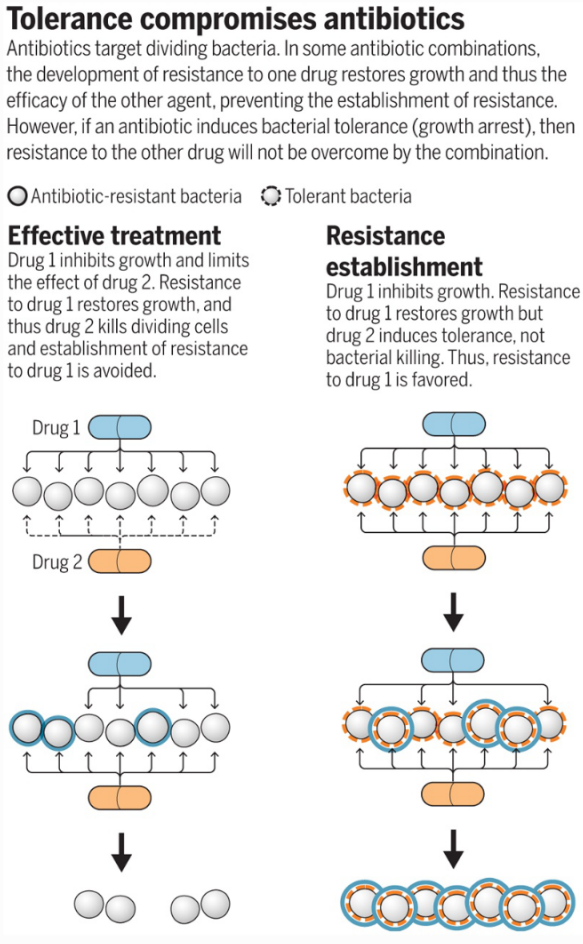
18.1.2. Why are drug combinations used in treating bacteral infections?

Generally, single antibiotic is rarely given, especially in chronic disease. More than one antibiotic is combined to form what is called a multi drug therapeutic regimen. When antibiotics are combined it may result in either synergistic or additive effect. The effect is due the action of the drugs at the targeted site, not because of interaction at the absorption, metabolism, protein binding and excretion level.

Reasons justifying the use of antimicrobial combinations:

- broad-spectrum coverage for the initial therapy of severely infected patients.
- polymicrobial infections (infection with more than one microbe , mixed bacterial infections); If the pathology is due to mixed infection then it is better and logical to use combined therapy.
- to reduce the risk of or overcoming bacterial

resistance when a high mutation rate of the causal organism exists to the antibiotic indicated. By combining drugs, you can prevent the resistance developing against the drugs or even if resistance develops against one drug, the other drug takes care of the resistant bacilli. Development of resistance against two drugs simultaneously is rare because you need large population of multiplying bacilli at the infection site to induce natural resistance, which is generally not the case. For example in the DS TB regimen, rifampicin takes care of subpulation of bacilli which may be resistant to ethambutol.



- reduction of dose-related toxicity – this concern is rare and mostly of

- historical interest, related to the use of sulfonamides; and
- antimicrobial synergistic activity particularly against resistant bacteria.
- By combining drugs it is possible to shorten the

period of treatment.

It is appealing to use combinations and treat two types of infections— infections resulting from resistant or relatively resistant organisms and infections requiring a bacterial eradication (high bactericidal effect), considering the site of infection and the host defenses.

18.1.3.What is synergism?

Synergistic effect is the situation where the combined effect of two chemicals is much greater than the sum of the effects of each agent given alone, for example:

2 + 2 >> 4 (maybe 10 times or more)

It is different from additive effect - this action occurs when the combined effect of two or more chemicals is equal to the sum of the effect of each agents given alone (they do not interact in a direct way); for example:

2 + 2 = 4

Why does synergism occur?

There are countless enzymes in the body which catalyse the breakdown of metabolites or synthesis of new molecules. It is these metabolites either intermediate or

final which regulate bodily functions. For example, there is an emzyme that breaks down alcohol (alcohol dehydrogenase) into acetaldehyde (a toxic molecule) which is broken down to acetate by acetaldehyde dehydrogenase. This is the reason people who consume alcohol do not remain intoxicated forever after consuming alcohol. These enzymes transform foreign substance into less toxic or nontoxic substances which are then eliminated from the body. Acetaldehyde produced when alcohol is acted upon by alcohol dehydrogenase can produce respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, fast heart rate, low blood pressure, fainting, marked uneasiness, weakness, vertigo, blurred vision, and confusion. This is taken advantage of to treat alcoholism where a drug called disulfiram is used. It inhibits conversion of acetaldehyde to acetate. Acetaldehyde accumulates and if a person on disulfiram consumes alcohol it causes symptoms mentioned above. This may prevent the individual from consuming alcohol.

Additive or synergistic effects are seen when antibacterial agents are used in combination. Prime examples are the combination of clavulanic acid with amoxicillin or ticarcillin (or sulbactam with ampicillin), in which the first agent prevents β-lactamase destruction

of the second agent, or the combination of a diaminopyrimidine such as trimethoprim or ormetoprim with a sulfonamide.

Ideally, antimicrobial selection should be based on different mechanisms of action and on complementary spectra of activity. β-Lactams are often selected, because their action may damage the cell wall and facilitate movement of other drugs into the microbe. Examples of combination therapy for mixed infections include the use of clindamycin, metronidazole, or the semisynthetic penicillins for their anaerobic coverage in combination with aminoglycosides for their gram-negative efficacy.

18.1.4. Why is treatment for tuberculosis prolonged?

Remember, antibiotics act only on actively multiplying bacilli. This is because their action is best when metabolic processes are occurring or the baby bacilli are being produced. The baby bacilli are yet to have cell wall and antibiotics with action on the cell wall can inhibit the formation of cell wall and kill them. Similarly, antibiotics which are active against protein synthesis act best when the bacilli are making proteins. The effect on protein synthesis may not result in immediate killing

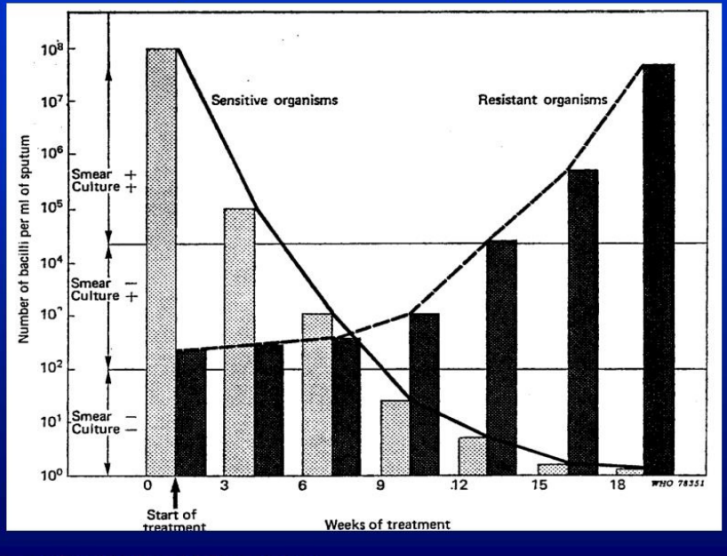
of the bacilli but results finally in their death.

As we know, M.tuberculosis is a slowly multiplying bacilli- it takes average 20 hours for M.tuberculosis to multiply and double its number compared to bacteria like streptococcus which reaches enormous numbers in just 5 hours.

Bacilli in the infected site are in various stages of growth. Some are actively multiplying and some are multiplying in spurts and others, lying inside macrophages, lie in a quiescent state stopping all metabolic activities. Antibiotics cannot act on these quiescent bacilli. You need different agents to act on bacteria in different stages of growth. It takes a long time to get rid of slowly multiplying or quiescent bacilli. We don't have antibiotics which can eliminate totally the quiescent or nonmultiplying bacilli. This is one of the reasons why treatment is prolonged.

Antibiotics kill rapidly multiplying bacilli. Those residing inside macrophages and are dormant are not killed. When the antibiotic is stopped,

Treating TB with one drug – Improvement then worsening – the fall and rise phenomenon



Source: Toman Case Finding and Chemotherapy

the quiescent bacilli start multiplying and cause relapse. By reintroducing the antibiotics the bacilli are killed unlike those bacilli which are resistant. This process is called fall and rise phenomenon. When the bacilli start multiplying if there is no antibiotic, then symptoms will recur. Short duration treatment may therefore increase the chance of relapse.

18.1.5. Why there are two phases in the treatment of tuberculosis

Generally, treatment strategy for tuberculosis involves two phases of drug therapy: the initial *intensive phase* and later *continuation phase*.
Intensive phase: more drugs are used for a shorter period to kill as quickly as possible all the actively multiplying bacilli and the objective is to prevent the emergence of drug resistance;
Continuation phase involves using less number of drugs for a longer period to kill the remaining bacilli especially the dormant ones and to sterilise the site of infection and prevent relapses.

At least four drugs likely to be effective compose the regimen, of which at least two are essential (or 'core' drugs), while two are companion drugs. The *core drugs* are those with the capacity to kill *M. tuberculosis* in any

of its metabolic phases. In contrast, the role of the *companion drugs* is to support the core ones, protecting their action and avoiding selection of further resistance. Whilst one of the core drugs should have a good bactericidal activity, the other should have a good sterilising activity, and they need to be maintained for the entire duration of treatment. While bactericidal drugs efficiently reduce the bulk of the rapidly multiplying bacilli (decreasing infectiousness and avoiding the disease's progression), sterilising drugs take care of the population of dormant and semi-dormant bacilli, allowing cure and preventing relapse. The best sterilising drugs may reduce the duration of the treatment while the companion drugs are no longer necessary after bacteriological conversion. When documented resistance or toxicity appears for a core drug, it should be replaced by another with a similar efficacy (bactericidal and sterilising). Similarly, an accompanying drug should be replaced by another with a similar action.

Take for example the regimen for drug susceptible TB. HRZE2/HR4. Two months of Rifampicin, INH, pyrazinamide and ethambutol and 4 months of INH, Rifampicin. During the intensive phase the actively multiplying bacilli are rapidly killed by INH and Rifampicin which are the core drugs. Pyrazinamide deals with bacilli multiplying in the acidic inflammatory

environment of the TB cavity. Ethambutol along with Pyrazinamide are the companion drugs. Four drugs out of which two are core and are bactericidal. After the intensive phase when the sputum is negative it is assumed there is very little inflammation at the site of infection. There is, therefore, little need for pyrazinamide. In the continuation phase we need at least two drugs to which bacilli are susceptible. Only two drugs are given in the CP. This is because the number of bacilli at the end of IP is very low, so the likelihood of resistant mutants being there is low.

18.1.5. What are the different regimens?

18.1.5.1. Drug susceptible Tuberculosis

A. Drug susceptible pulmonary TB - 6 months regimen

2HRZE/ 4 HR

Daily dose regimen
Rifampicin throughout
2 months intensive and 4 months continuation phase
If positive at the end of IP, no extension but switch to drug resistant tb treatment
Fixed dose combinations

B. Drug susceptible nonsevere TB without suspicion or evidence of drug resistance- 4 months regimen-

2HRZE/2HR

Age 3 months to 16 years

C. Drug susceptible pulmonary TB- 4 months regimen

2HPMZ/2HPM

HR(rifapentine)M(moxifloxacin)P (Pyrazinamide)
INH, Rifapentine, Moxifloxacin, Pyrazinamide

For patients 12 years and above

18.1.6. Drug resistant tuberculosis

- The combination should have drugs with different sites of action: a good combination of cell wall inhibiting and protein synthesis inhibitors is preferred.

- Drug with sterilising action and capable of acting on quiescent bacteria(action preferably on ATP)
- All drugs except Rifampicin used in the treatment of DS tuberculosis are included in the regimen.

Group	Class of drugs		Drugs
Group A	Fluoroquinolones		Levofloxacin
			Moxifloxacin
			Gatifloxacin
Group B	Second-line injectables		Kanamycin
			Amikacin
			Capreomycin
Group C	Other core second-line agents		Ethionamide/Prothionamide, Cycloserine/Terizidone, Linezolid, Clofazimine
Group D	Add-on agents	D1	Pyrazinamide
			Ethambutol
			High-dose isoniazid
		D2	Bedaquiline
			Delamanid
		D3	P-aminosalicylic acid
			Imipenem-cilastatin
			Meropenem
			Amoxicillin-clavulunate
			Thioacetazone

- Since majority of antibiotics are derived from bacteria they are likely to develop resistance. Drugs which are not based on bacterial metabolites like clofazimine are less likely to develop resistance.
- Drugs with wider therapeutic window (less toxic) are preferred
- Injectables are used only when the programme has a good system to monitor oto- and vestibular toxicity.
- Fluoroquinolone is the first choice for replacing rifampicin. Among the fluoroquinolones, levo and moxifloxacin are the ones which are preferred because of their less potential to produce serious toxic effects.
- Choice of drugs depends also on the health status of the patient. Drugs with potential to cause hepatic, renal, cardiac or neurological toxicity effects are contraindicated or used with caution in

the presence of condition related to the organs likely to be affected by the drugs.

- Administer at least 5 drugs for the intensive phase of treatment and at least 4 drugs for the continuation phase. One fluoroquinolone (group A), none from group b (rarely to be used), two drugs from group C (ethionamide, cycloserine / ethionamide and linezolid/ linezolid and clofazimine) and both the drugs in group D2 (Bedaquiline and pretomanid). When two drugs cannot be included from C and D2, then choice will be one of the drugs from D3 (PAS/ Augmentin/ meropenam).
- Depending on the combination of drugs, the duration of treatment can be 20 to 24 months, 9 months or 6 months. Inclusion of fluoroquinolone, bedaquiline, pretomanid and linezolid allows shortening the duration of regimen. But the price we pay is in terms of toxicity. Shorter regimen is good for patients and providers.
- Antitb drugs used in drug resistant tuberculosis are grouped under 6 groups. Grouping has been revised recently, the number has changed from 5 to 6 groups. The basis for grouping does not seem to be entirely rational. I would like to see grouping based on mechanism of action, efficacy, side effects in that order.

- I will not go into the details of different regimens because they are continuously evolving. The principle is to include at least two drugs which acts on cell wall synthesis and therefore are rapidly bactericidal, and two which act on protein synthesis, and one with multiple sites of action. At least one of the drugs should have sterilising action capable of getting rid of quiescent bacilli.

(Drugs acting on cell wall synthesis

INH
Ethambutol
Ethionamide, Prothionamide
Cycloserine
Delamanid
Augmentin

Drugs acting on protein synthesis

Rifampicin
Fluoroquinolones
Aminoglycosides
Linezolid
Bedaquiline
PAS

Drugs with multiple sites of action

Pyrazibamide
Pretomanid
Clofazimine

- Finally, there is a need to have only two regimens, one for DS tuberculosis and the other for drug resistant tuberculosis. I would also avoid the distinctive two phases in the regimen because the rational for this is not clear (except to limit the period of administration of potentially toxic drugs).