Chemotherapy; Antimicrobials

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LECTURE 02 NOTES

MO:microorganism,,,AM:antimicrobial,,,some abbreviations u may see in slides must know them before starting.

✓ Classification of antimicrobial:

According to:

- Mechanism of action How the AM acts on the cell wall of bacteria or How it affects the protein synthesis of MO.
- Chemical structure . the specificity of the chemical structure of AM with its microbe when binding
- Antimicrobial activity (spectrum of activity):
- Narrow spectrum (effective in G+ve cocci * bacilli), drugs effective in G-ve bacilli & cocci such(Aminoglycosides), drugs only effective inspecific infection (Isoniazid is only active against mycobacteria T.B)

NARROW spectrum means that the AM covers little types of microbes inits infection

,,,BROAD covers more types than NARROW

* * Broad spectrum (effective in G+ve & -ve cocci & bacilli)

Affect a wide variety of microbial species (this type could alter the nature of the normal flora & (precipitate a superinfection

* Extended-spectrum antibiotics

Agents that are effective against gram-positive organisms & also against a significant No. of gram-negative bacteria or against specific microorganisms EXAMPLE FOR ANTIMICROBIALS SPECIFIC TO MO:

e.g. Antipseudomonal penicillins

Of course the more the antibiotic related to(specific to) . MO ,the more its activity in infecting it..

we must ask if its critical to use the AM here or not.because in SOME viral infections(common cold),bacterial,fungal infections ^^ .its not critical to use AMs,you can use some grandmothers herbs.

✓ General considerations in the usage of antimicrobials: :antimicrobials

- Is the antimicrobial agent indicated
- Aim if indicated is to achieve a level of antimicrobial activity at the site of infection that is sufficient enough to inhibit or kill microorganisms without affecting host cells

✓

,,,,,More clarifications for the last point in the next page

To increase our knowledge for a certain drug and to know the conrn that :after it the toxicity will appear we must.

1 Inject this AM to animal experiments and take our notes.

2 We must see its effect on humans to be sure that its outcomes is the same to the outcomes that we noticed on animals and see the pharmacokinetics after taking this AM.

And remember that we must proceed the 4 phases of clinical* .investigations for this AM in the population
that we took them with Dr.Alia.

- Antimicrobials are harmful drugs
- New drugs are not necessarily better than old ones
- Major consideration is identification of the causative microorganism and the use of proper dose for adequate duration
- Sometimes there is a need to combine more than one antimicrobial

- ✓ :Selection of an antimicrobial agent

:Factors affecting selection

1. Causative microorganism (susceptibility): "The lack of susceptibility guarantees therapeutic failure".
   Determined from:
   - -Clinical picture (Empiric therapy: the use of an antibiotic prior to identification of organism in critically ill patients
   - - Bacteriological examination (culture and sensitivity)
   - - Serology-measures antibody levels
   - -Polymerase Chain Reaction (PCR) detects the specific DNA for a specific organism

- clinical picture: the symptoms that are related to the MO such as in some infections (headache,strictness of leg...etc).

- Bacterial examination: here we take sample from the effected organ for example we take from the CNS a CSF sample and culture the MO then we study its reaction with our AM and see results. After that we can see the sensitivity of that MO to our AM ,is it sensitive or not?! Usually if the results of your study improved your expectations in inhibiting or killing the MO your patient starts to feel good from your AM.

  Sometimes you give him an antibiotic and he starts to improve but your results found that there is no sensitivity of the MO to your drug, regard the results and proceed with your patient with this drug.
  And this using before the sensitivity results is called "Empiric therapy"
  And sometimes the results say that there is sensitivity but the patient is not improving with that AM.

- Serology:here we measure specific antibodies presented on the surface of cells, and sometimes we measure specific antigens as we took in VIRO.

- PCR:used to study a specific DNA for specific MO. The most used method is "cultural sensitivity". If it failed we use the others.

Illustration is on the next page

2. Pharmacokinetic factors:

Site of infection CNS, prostate, vitreous body of eye…

Renal disease (poor kidney function cause antibiotics that ordinarily secreted by this route to accumulate & lead to serious adverse effects e.g. aminoglycosides)

:PHARMACOKINETIC FACTORS

There is some difficulty in antibiotics in entering certain organs such as "CNS,PROSTATE,VITREOUS BODY OF EYE".

So giving the patient the drug orally or parentally or IV will not be benefit for such organs
So if the target organ is CNS we inject him by intrathecal method locally to reach the CSF(Cerebrospinal Fluid).

Also in renal diseases we must not give him antibiotic that the kidney excrete it, so we rather change the antibiotic to one that excreted by the liver
OR
to reduce the dose of this antibiotic such (aminoglycoside)
that its very toxic to the kidney.

The same idea as RENAL disease

Liver disease (antibiotics that are concentrated or eliminated by liver are contraindicated in liver disease (e.g. erythromycin & tetracycline).

Route of administration

3. Toxicity and side effects to antibiotic
4. Interactions with other drugs
5. Cost

Route of administration:

- ✓ Toxicity and side effects to antibiotic that does not tolerate

There is specific side effects for specific antimicrobial agent, so you must use another drug.

- ✓ Interactions with other drugs: in old people who take 9 drugs we can have some serious interactions that cause bad effects and can be lethal

So if there is such these interactions "change the antibiotic that interact with the other or tell your patient to take him separately"

allergic reactions is a reverse side effects that almost all the antibiotics can cause it! so u should not give the patient an AM .that can cause allergy for him

6. Host factors

*Age (newborn & old pts have less kidney and liver function compared to adults) usually when the age increase more antibiotics will be taken

*Allergic reaction to a given antimicrobial agent

,Host defense mechanisms (alcoholism, DM ,HIV, malnutrition, poor hygiene, advanced age neutropenia, & the use of immunosuppressive drugs can affect a patient's immuno-competency Such patients need higher-than-usual doses or (longer courses of treatment).

decrease WBC

cRemember that we have cidal and static AM and that cidal is more defect than static. But we usually use cidal.

So if one has mutated,abscent,abnormal G6FDehydrogenase and these antibiotics given to him--->hemolysis,,,,,if he takes more---> severe hemolysis---> immediate death.

OR during pregnancy we give mothers iron supplements to accommodate with this decrease of RBC

7. Genetic factors

– Sulfonamides, chloramphenicol, nitrofurantoin→ severe hemolysis in G6PD deficient individuals

8. Pregnancy: Streptomycin → Deafness

9. Lactation: is the process to produce milk in the breast for breast feeding for infants

Sulfonamides → hemolysis in G6PD deficient newborn These antibiotics should NOT given while breast feeding affected infants! and they cant cause infection in normal born infants.

10. Local factors at site of infection: e.g. abscesses

antibiotics could not reach abscess so we must make drainage to release the pus so the antibiotic can reach.

✓ **:Bacterial resistance**

:Occurs

- **When clinical condition of host is impaired**
- **When normal flora have been suppressed**
- **With interrupted or inadequate Rx**
- **More frequently in certain types of bacteria (Gram negatives possess an outer membrane and cytoplasmic membrane preventing passage of (antibiotic through pores** usually some antibiotics translated proteins try to enter, no entering---> increasing bacterial resistance
- **With widespread use of broad spectrum antibiotics**
- **In poor environmental setting of host. (**Poor hygiene,poor sanitation can increase the resistance)

Mechanisms of bacterial resistance

- Natural resistance

- Absence of a metabolic process or an enzyme or protein in the bacteria which is required for the action of the antimicrobial

  For example: sulfonamides cant do its function if the bacteria does not have or has abnormal synthase enzyme of DHFA DiHydroFolic Acid

- Absence or hard cell wall making the antimicrobial difficult to penetrate

  Absence: such mycoplasma

* The need of antimicrobial drug in large amounts at site of action above its concentration in the plasma

There proper AM must has high MBC,MIC to kill it

To overcome this type of resistance the drug has to be given in very large doses which leads to severe side effects

- Acquired resistance Development of resistance in a previously sensitive microorganism. This could occur in the following ways:
- - Mutation or genetic change
- - Adaptation
- Production of enzymes breaking the antimicrobial e.g. β-lactamases

B-lactamase hydrolysis B-lactam of the AM,such cephalosporinase inhibit cephalosporin

- Infectious or multiple drug resistance

:Through

Transduction by bacteriophage which transfers chromosomal or ."extrachromosomal DNA (plasmid) to bacteria."this gene can be resistant gene

Transformation, transfer of DNA responsible for resistance from environment to ."bacteria."that also can be resistant gene

- Conjugation Passage of resistant genes from cell to cell by direct contact

** Most of resistance is acquired due to misuse or abuse of antibiotics e.g. improper dose & DOA, Rx of suppurative diseases, Rx of viral infections with antibacterial agents

Duration Of Action

The most important type of bacteria in such resistance isthe "normal flora bacterias

penicillin binds to specific proteins present on some susceptible"sensitive\not resistant" MO .called PBP(penicillin binding protein),so altering structure can cause resistance

✓ :Examples of resistance

- Generating enzymes that inactivate the antibiotic (beta lactamase)
- Changing structure of target site e.g. PBP's (beta lactams and aminoglycosides)
- Preventing cellular accumulation of antibiotic by altering outer membrane proteins or using efflux pumps e.g. G-ve

For example tetracyclines

We have DNA repair mechanisms for some bacteria that can use it when some AM affects its DNA .(same idea when cancerous cells repair its DNA against its anticancer agents)

- Changing the metabolic pathway that is being blocked (sulfa drugs)
- Overproducing the target enzyme to overpower the effects of antibiotics

more proteins-->high dose, increase side effects

- Mycoplasma lacks a cell wall making it resistant to penicillins
- Sulfonamides have no impact on bacteria that obtain their folate from environment

:combined therapy

:Indications

To obtain synergism(combine your AM with other specific drug - increasing the activity of the first one"1+1=3") or reduce the dose of a .toxic drug

- To reduce emergence of resistance

In some MO such myco. TB we must combine because they are rapid resistace MO so rather we give him 3or 2 drugs and then we drop one and continue with the other for
.years.

- :Treat mixed infections with microorganisms of differentsensitivities

Its better to use one antibiotic that can treat these infections
.if its not offered we combine 2 drugs.

- Treat infections at different anatomical sites (bile, CSF) Its better to use 1 antibiotic that can reach both if its not offered we combine 2 drugs

- Treat infections of unknown etiology especially in patients at high risk of developing infections e.g. AIDS patients or patients with agranulocytosis

That affect the granulocytes(lymphocytes.monocytes)

Outcome of combined chemotherapy:

- Indifference ."no effect of one drug on the other when comined"

- Antagonism (Cidal + static)they said that combing them can reduce the activity of the CIDAL!!

- Synergism (Penicillin + aminoglycosides):

aminoglycoside--->affects synthesis of proteins
penicillins--->affects the cell wall of MO.

so penicillin's help aminoglycosides in its function تآزر.

Disadvantages of combined chemotherapy:

- Toxicity
- Cost

■ Prophylactic use of antibacterial agents:

Indications:

- Protection of healthy individuals against highly contagious disease or infections e.g. syphilis, gonorrhea, T.B, meningococcal meningitis.

Here we must provide Protection, by providing them with the appropriate vaccines as prevention and treatment if the disease occurred

- Prevent 2º infection in very ill patients e.g. AIDS, before major surgeries, delivery, organ transplantation, recurrent UTI's…etc

■ **Prophylaxis is successful if:**

- A single antibiotic is used.

- The dose required for prophylaxis is less than the therapeutic dose.

- The drug is needed or used for a brief period (chronic therapy or prophylaxis is not advised → bacterial resistance).

■ Complications of antibiotic therapy:

- Hypersensitivity "never ever penecellins given IV in allergic pateints"
- Direct toxicity "specific toxicity"
- Super infection.

Alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.

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