TUBERCULOSIS TREATMENT.
WHAT IS NEW?
TUBERCULOSIS

Today, tuberculosis is a pressing medical and social problem for the whole world.

According to world statistics, 2 million people die of tuberculosis every year. WHO estimates that between the years 2000 and 2020, almost a billion people will be infected, 200 million will be diseased, and 35 million will perish of tuberculosis, unless more stringent epidemic control is exercised.

The most common tuberculosis form is pulmonary tuberculosis, associated with bronchopulmonary syndrome (dry or wet cough, chest pains during breathing, blood spitting, pneumorrhagia) and toxic syndrome (fever, weight loss, loss of appetite, increased sweating, weakness).

In 2006 “The stop TB strategy” was created by WHO

1. Pursue high-quality DOTS expansion and enhancement;
2. Address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations;
3. Contribute to health system strengthening based on primary health care;
4. Engage all care providers;
5. Empower people with TB, and communities through partnership;
6. Enable and promote research.
   - Conduct programme-based operational research
   - Advocate for and participate in research to develop new diagnostics, drugs and vaccines.

DRUG-RESISTANT TUBERCULOSIS - PRINCIPAL REASON OF UNEFFECTIVENESS OF TREATMENT

From data of WHO, In some areas of the world, one in four people with tuberculosis becomes ill with a form of the disease that can no longer be treated with standard drugs regimens. For example, 28% of all people newly diagnosed with TB in Russia had the multidrug-resistant form of the disease (MDR-TB) in 2008. This is the highest level ever reported to WHO. Previously, the highest recorded level was 22% in Baku City, Azerbaijan, in 2007.


Multidrug-resistant TB (MDR-TB) is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs. MDR-TB results from either primary infection with resistant bacteria or may develop in the course of a patient’s treatment. Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to isoniazid and rifampicin as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin or capreomycin). These forms of TB do not respond to the standard six-month treatment with first-line anti-TB drugs and can take up to two years or more to treat with drugs that are much more expensive.

Overcoming of drug resistance of MTB and warning of it's distribution - one of main tasks of the system of health protection
**INCREASING TUBERCULOSIS TREATMENT EFFECTIVENESS**

Most essential is an intensive phase of chemotherapy of tuberculosis, a basic task of which is maximally possible elimination and suppression of height and reproduction of population of MTB in the organism of patient.

**Exactly in this phase especially important:**
- 100% treatment controllability;
- Intensification of therapy;
- Overcoming of drug resistance of MTB and warning of it’s distribution.

**Only intravenous introduction of preparations provides implementation of the put tasks and promotes efficiency of therapy.**

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**Intravenous administration ensures:**
- Intensification of therapy*
- 100% bioavailability of drugs
- 100% treatment controllability
- Prevention of MBT resistance development**
- Decreased risk of digestive tract side effects
- Improved tolerance to chemotherapy.

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**“YURiA-PHARM” antituberculosis drugs for intravenous administration**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmaceutical form</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line antituberculosis drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifamycin (R) RIFONAT</td>
<td>Vials</td>
<td>concentrate for infusion solution preparation, 150 mg 450 mg, 600 mg</td>
</tr>
<tr>
<td>Ethambutol (E) INBUTOL</td>
<td>Vials</td>
<td>10% Injection/infusion solution, 10 ml, 20 ml</td>
</tr>
</tbody>
</table>

| **Second line antituberculosis drugs** |
| Ofloxacin (Ofx), Ciprofl oxacin (Cfx), Levofloxacin (Lfx) LEFLOCIN, Gatifloxacin (Gfx) BIGAFLON, Moxifloxacin (Mfx) MAXICIN | Vials, bags infusion solution Vials, bags infusion solution Vials, bags infusion solution Vials, bags infusion solution Vials, concentrate for infusion solution preparation | 200 mg/100 ml, 400 mg/200ml 200 mg/100 ml, 400 mg/200ml 500 mg/100 ml, 750 mg/150 ml, 1000 mg/200 ml 400 mg/100 ml, 800 mg/200 ml 400 mg/20 ml in a complete set with a solvent |
| PAS (PAS) PASKONAT  | Vials               | 3% infusion solution 3% (12 g/400 ml)                                  |

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*intravenous administration ensures that the drugs reach the disease loci before being biotransformed in the liver, therefore achieving a higher clinical effect.

**Creation of high concentrations of preparation in blood and tissues is able to overcome resistance of MTB.**
DRUG BIOAVAILABILITY

Any administration method save for intravenous results in only a part of the drug dose reaching the systemic circulation, due to incomplete absorption, destruction at the administration site caused by specific and non-specific enzymes, non-optimal pH, and, in case of oral administration, also due to the effect of the first liver transit.

Drug bioavailability directly determines the effectiveness of treatment.

The bioavailability of drugs administered intravenously is always 100%.

Factors determining drug absorption:
- absorption surface area;
- environment pH;
- hydration and hemoconcentration rate;
- microcirculation condition.

NB! All of the above factors are patient-specific. It is impossible to provide for all of them for every contingency.

One of the principles of tuberculosis chemotherapy is administration of the entire daily dose in one go, which ensures the maximum possible drug concentration for maximum effect on the MBT. Of all methods, intravenous administration provides for this.
METHODS TO INCREASE TUBERCULOSIS TREATMENT EFFECTIVENESS

According to the research conducted by the National Phtisiology and Pulmonology Institute of the Academy of Medical Sciences of Ukraine named after F. Yanovksiy, tuberculosis treatment effectiveness can be increased by 20-30% by using the following methods:
- Intermittent administration of high doses of pyrazinamide and ethambutol (Inbutol 20.0, IV drip, every other day);
- Use of fluoroquinolone-based antibacterial drugs (levofloxacin (LEFLOCIN), gatifloxacin (BIGAFLON), moxifloxacin (MAXICIN)).

Today, the effectiveness of fluoroquinolone-based antibacterial drugs against MBT is considered equivalent to such first-line drugs as ethambutol and pyrazinamide.

The experience of Russian phthisiology*

Treatment of patients with new-onset destructive tuberculosis is carried out using a standard 1st chemotherapy regimen which includes isoniazide, rifampicine and streptomycin or ethambutol. According to the data of Russian researchers, in the period from 2003 to 2006, treatment with the above regime resulted in ceased bacterioexcretion in no more than 73.5% of new patients, and elimination of cavitary lesions in the lungs in 63%.

The low effectiveness of chemotherapy in patients with new-onset destructive pulmonary tuberculosis is associated with the primary drug resistance of MBT.

Order of the Ministry of Health Care of the Russian Federation of 21.03.2003 determines chemotherapy regimen 2b, which consists of a combination of isoniazide, rifampicine, ethambutol, fluoroquinolone (levofloxacin, gatifloxacin, moxifloxacin, ofloxacin, ciprofloxacin) and kanamycine or amikacin.

The decisive role in the effectiveness of regimen 2b is played by fluoroquinolones.

Such drugs as ciprofloxacin, ofloxacin, levofloxacin (Leflocin), moxifloxin and gatifloxacin (Bigaflon) have a bactericidal effect on MBT. They also have a synergistic and/or additive effect on rifampicine, isoniazide, pyrazinamide and ethambutol.

<table>
<thead>
<tr>
<th>Patients group</th>
<th>Number of patients</th>
<th>Of which MTB(+)</th>
<th>Ceased bacterioexcretion (months)</th>
<th>MTB(+) after 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Regimen 2b</td>
<td>Абс. 30</td>
<td>30</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>% 100</td>
<td>100</td>
<td></td>
<td>73,3</td>
<td>23,3</td>
</tr>
<tr>
<td>Regimen 1</td>
<td>Абс. 30</td>
<td>30</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>% 100</td>
<td>100</td>
<td></td>
<td>53,3</td>
<td>13,3</td>
</tr>
</tbody>
</table>

PROPHYLAXIS OF TUBERCULOSIS

Children - one of the most vulnerable groups on a risk to become ill tuberculosis.

In the conditions of worsening of epidemic situation for children from the groups of risk the effective method of his warning continues to remain chemoprophylaxis.*

Necessity of chemoprophylaxis

There are data, that the prophylactic use of antituberculosis preparations at the infected persons in 5-9 times reduces their risk to become ill in the future.

For realization of prophylaxis in most cases isoniazid is used in a dose 5-8 mgs/kg of mass of body of child. Duration of prophylaxis makes from 2 to 6 month.

Reasons of uneffectiveness of chemoprophylaxis:

- subzero doses of antituberculosis preparations;
- insufficient terms of prophylactic treatment;
- irregular reception of preparations;
- breaking of course of treatment;
- realization only of one course of prophylaxis instead of shown a few;
- realization of prophylaxis to the children and teenagers from the hearths of tubercular infection without the account of spectrum of resistance of MTB to antituberculosis preparations at the sources of infection.

Realization of chemoprophylaxis with the use of isoniazid in pharmaceutical form of syrup

PLUSES

• Lightness and exactness of dosage even for a baby
  (1 ml of syrup = 20 mgs of Isoniazidum);
• Minimized risk of side effects;
• Less irritating operating on the mucous membrane of a gastro-intestinal system;
• Maximal compliance to prophylaxis as from the side of child:
  - it is preparation sweet with a fruit smell,
  - negative attitude is not created toward treatment,

so from the side of parents:
- syrup is psychologically perceived easier, than pill,
- there is not a necessity to execute specific actions to give preparation to the child - to press a pill, mix up with food etc.

*Моисеева О.В. Проблемы химиопрофилактики туберкулеза (обзор литературы). РМЖ. февраль 2009 г, том 17, № 2
ISONIAZIDUM
(100 mg/5ml syrup)
- Accurate dosing
- Convenient administration
- Pleasant taste and smell
- Lower risk of side effects

Registration Certificate of Ministry of Health of Ukraine № UA/4667/01/01 dated 23.05.06.
Registration Certificate of Ministry of Health of Uzbekistan № 54108 dated 21.11.08.
Registration Certificate of Ministry of Health of Tajikistan № РС-004324 dated 04.09.08.

INBUTOL
(ethambutol hydrochloride, 10% infusion solution)
- 100% controllable therapy
- Maximal efficiency
- Maximal safety

Registration Certificate of Ministry of Health of Ukraine № UA/4739/01/01 dated 20.07.06.
Registration Certificate of Ministry of Health of Uzbekistan № 59308 dated 07.11.08.
Registration Certificate of Ministry of Health of Republic of Moldova № 15687, 15688 dated 05.08.10.
Registration Certificate of Ministry of Health of Tajikistan № РС-004323 dated 04.09.08.

RIFONAT
(30 mg/ml rifamycin concentrate for preparation of infusion solution)
- One of the most effective antituberculosis drugs
- Infusion administration provides for the highest effectiveness of treatment
- Lower risk of gastric side effects
- Overcome resistance of MTB

Registration Certificate of Ministry of Health of Ukraine № UA/11420/01/01 dated 23.03.11.
Registration Certificate of Ministry of Health of Republic of Moldova № UA/8132/01/01 dated 04.04.08.
Registration Certificate of Ministry of Health of Russia № РК-ЛС-5-№009664 18.01.06.
Registration Certificate of Ministry of Health of Azerbaijan № DV№08-02288 25.12.08.
Registration Certificate of Ministry of Health of Tajikistan № ЛС-003260 30.07.07.
Registration Certificate of Ministry of Health of Uzbekistan № 48708 24.10.08.
Registration Certificate of Ministry of Health of Russia № РК-ЛС-5-№009664 18.01.06.

PASKONAT
(paraaminosalicylic acid, 3% infusion solution)
- Long history of use in tuberculosis treatment
- Low development of MBT resistance
- Increases effect of other antituberculosis drugs

Registration Certificate of Ministry of Health of Ukraine № UA/8132/01/01 dated 04.04.08.
Registration Certificate of Ministry of Health of Russian Federation № РК-002960 dated 29.12.06.
Registration Certificate of Ministry of Health of Uzbekistan № 48708 dated 24.10.08.
Registration Certificate of Ministry of Health of Republic of Moldova № 14851 dated 10.12.09.
Registration Certificate of Ministry of Health of Tajikistan № РС-003260 dated 30.07.07.
Registration Certificate of Ministry of Health of Azerbaijan № DV№08-02288 25.12.08.
Registration Certificate of Ministry of Health of Kazakhstan № РК-002960 dated 18.01.06.

“YURIAPHARM” antituberculosis drugs - controllability and effectiveness!