Application for the inclusion of rifampicin for intravenous use (addition – new formulation/strength of existing medicine) in the in the WHO Model List of Essential Medicines and Model List of Essential Medicines for Children, section 6.2.4 as a first-line drug for the treatment of tuberculosis in severely ill patients and those who have absorption disorders as a lifesaving possibility to receive proper anti-tuberculosis treatment

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1. Summary statement of the proposal for inclusion, change or deletion

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB).

Every year, 10 million people fall ill with tuberculosis (TB). Despite being a preventable and curable disease, 1.5 million people die from TB each year – making it the world's top infectious killer [46].

TB is the leading cause of death of people with HIV and also a major contributor to antimicrobial resistance, which means the urgent need in additional efforts to study the main reasons of treatment failure and additional efforts to save those 1.5 million lives per year.

Among all TB deaths, 77.2% of patients die during intensive phase of treatment and 36.4% of patients die in the first 10 days of the treatment, according to recent studies. [7, 11-12] That means, severe TB patients are in the blind zone of the standard TB care and require additional treatment efforts, for example hospitalization and using anti-TB preparations with immediate action, such as intravenous drugs instead of tablets.

Rifampicin is one of the most effective chemotherapeutical component that is present in main treatment regimens of drug-susceptible tuberculosis recommended by WHO.

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations. [1]

The EML and EMLc already contain preparations of oral rifampicin. This application proposes IV rifampicin for the core list of the WHO Model List of Essential Medicines and Model List of Essential Medicines for Children, as a lifesaving medicine for the following categories:

1. Patients with severe forms of tuberculosis with poor outcomes, requiring intensive treatment (Miliary TB [35,36], caseous pneumonia[37], TB meningitis [13], TB sepsis [38-39], TB pericarditis [42]).

2. Patients with acute or chronical gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [18-22]).

3. Patients with severe comorbidities: HIV/TB, diabetes/TB [43], etc.

4. Patients that are unable (unconscious patients in ICU or in coma [7, 44]) or

unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [16]

Currently, intravenous rifampicin is not available on most of the markets. The absence of IV rifampicin in both EML and EMLc leads to low interest in production of this dosage form and prevents the addition of it in tender drug lists of national and international TB programs.

2. Name of the focal point in WHO supporting the application

Dr Ernesto Jaramillo, MDR-TB Policy & Innovations department, World Health Organization Geneva, Switzerland

Bernadette Cappello, Secretariat, Essential Medicines List, World Health Organization Geneva, Switzerland

3. Name of the organizations consulted and supporting the application

International Union Against Tuberculosis and Lung Disease (The Union), National institute of phthisiology and pulmonology named after F.G. Yanovsky NAMS of Ukraine,

CU Communicable Diseases Intensive Care Association “Incure”, Ukraine,

Higher State Educational Establishment "Bukovinian State Medical University", Ukraine,

Novosibirsk TB Research Institute (NTRI), Russian Federation,

Universitas Padjadjaran Department of Pharmacology therapy, Indonesia, Clinical Research Unit and Institute of Biomedicine/Center for Global Health,

Universitatea de Medicină şi Farmacie „Grigore T. Popa” Iaşi, Romania. "Marius Nasta" Pneumoftiziology Institute, Romania

4. International non-proprietary name of the medicine e (INN, generic name) of the medicine

RIFAMPICIN

ATC code: J04AB02

5. Formulation proposed for inclusion

Formulation: solution for infusion/concentrate for solution for infusion,

Strength(s): 600 mg/vial

Indication: treatment of susceptible tuberculosis in combination with other first-line drugs

Addition – new formulation/strength of existing medicine

The EML and EMLc already contain preparations of oral Rifampicin. This application is for the additional inclusion of an intravenous (IV) preparation of Rifampicin 600 mg, powder for injections.

600 mg of Rifampicin is currently maximum recommended daily dose and it can be used as a fast and well-tolerated remedy for severe cases of tuberculosis. According to different sources, triple dose of rifampicin can be used combined with other TB drugs for 30 days for the treatment of TB meningitis, showing survival benefit with no significant damage to patient's safety. [2-4]

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Listing is requested as an individual medicine. According to WHO Guidelines, first line drugs for the treatment of susceptible tuberculosis (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) are widely available in their oral forms, however are not yet presented as IV preparations.

7. Treatment details (requirements for diagnosis, treatment and monitoring).

According to WHO guidelines [5], IV formulations should be reserved for cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis. [6]

IV. rifampicin is also recommended for use by American Thoracic Society. [6] I.e. IV rifampicin should be considered for the patients with severe forms of the disease (TB meningitis, TB sepsis), patients with acute or chronical gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [18-33]). Patients that are unable (unconscious patients in ICU or in coma [6]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [16] Patients with severe comorbidities: HIV/TB, diabetes/TB [44], etc.

Necessary conditions for intravenous infusion of anti-tuberculosis preparations:

- Placement of an implanted port or peripherally inserted central catheter (PICC) line (a non-tunneled venous catheter)
- Using intravenous (IV) therapy to infuse injectable drugs for 30 to 60 minutes, 5 days per week
- Direct observation of ingestion of prescribed oral anti-TB drugs
- Monitoring for adverse reactions and reporting these to the supervising physician
- Extensive patient education and support to help ensure adherence

IV therapy may be given via an implanted port (placed surgically under the skin, usually in the chest) or by PICC line (placed in the forearm and threaded into the superior vena cava). Both methods have their advantages and disadvantages, and the choice is usually made by the physician based upon the needs of the patient. [51]

8. Information supporting the public health relevance Epidemiological information on disease burden

Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million (range, 1.1–1.3 million) TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths (range, 177 000–242 000)6 among HIV-positive people (a reduction from 678 000 in 2000). Men (aged under 15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged under 15) for 12%. Among all those affected, 8.2% were people living with HIV. [45]

Among all TB deaths, 77,2% of patients die during intensive phase of treatment and 36.4% of patients die in the first 10 days of the treatment, according to recent studies. The fact of death from tuberculosis is usually confirmed in Intensive care unit (ICU). [7]

Assessment of current use

According to WHO guidelines for susceptible tuberculosis treatment, both pulmonary and extra-pulmonary forms of drug susceptible TB have to be treated with daily dosing of 6-month rifampicin-based regimen 2HRZE/4HR, with the only difference that adjuvant corticosteroid therapy should be considered in case of TB meningitis [46] .

According to the last WHO Model List of Essential Medicines (2019), only oral forms of first line anti-tuberculosis drugs are included [8].

Target population(s)

Several studies show that there is a decrease in the functional absorptive area of the intestine in TB patients, which would explain the reduced serum concentrations of anti-tuberculosis drugs. Patients with malabsorption syndrome don't get the minimum therapeutic level of anti-tuberculosis drugs, therefore such patients have to be treated or with higher doses of these drugs, what will cause higher level of adverse reactions from gastrointestinal system, or another dosage form should be considered. [9-10], [23-33]

Although most HIV-infected patients with tuberculosis (TB) respond well to rifampin-based anti-mycobacterial drug regimens [17], recent reports suggest that malabsorption of anti-mycobacterial drugs occurs in selected HIV-infected patients, particularly those with advanced HIV infection [18-22].

Up to 70% of admissions to ICU with active tuberculosis have acute respiratory failure (ARF) and require mechanical ventilation. [11-12] Mortality rate for such patients according to a retrospective cohort study in Brazil is up to 80%. [9] The causes of ARF in most of the cases are miliary lesions in lungs.

Other causes of TB death are Mycobacterium tuberculosis sepsis in immunocompromised patients, tuberculous pericarditis [42] and tuberculous meningitis [37].

Tuberculous meningitis (TBM) is one of the most devastating manifestations of extra-pulmonary tuberculosis (TBEP) and is associated with severe morbidity and high mortality up to 80% of cases. [13]

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

Injectable first line drugs for TB treatment are not available in most of the countries. However, IV forms ensure the quickest and the most complete access of the medicinal substance to the foci of TB infection.

Rifampicin peak plasma concentrations range reaches 8.9 mcg/ml when Rifampicin is given orally, comparing to the peak of 22.9 mg/ml when Rifampicin is introduced by intravenous infusion. [34]

Intravenous anti-TB drugs are essential for treating different categories of TB patients, including those with severe disseminated and gastrointestinal TB for whom oral anti-TB agents alone might not be effective. In some cases, this is caused by quick decomposition of the drugs during their relatively slow intake from the gastrointestinal tract and, in others, by the impossibility of increasing the dose. In the case of intravenous administration, the drugs are easily absorbed, which leads to the creation of higher concentrations in the infected tissues. [14]

10. Review of harms and toxicity: summary of evidence on safety.

HUMAN EXPOSURE: The main target organs are the liver and the gastrointestinal system. Risks of concern are toxic hepatitis with elevation of bile and bilirubin concentrations, anaemia, leukopenia, thrombocytopenia and bleeding. Summary of clinical effects: Some clinical manifestations of overdosage are extension of adverse effects. During therapy, rifampicin is usually well tolerated, however, adverse side-effects are common in intermittent rifampicin intake. These include febrile reaction, eosinophilia, leukopenia, thrombocytopenia, purpura, hemolysis and shock, hepatotoxicity and nephrotoxicity. Gastrointestinal adverse reactions may be severe leading to pseudomembranous colitis. Neurotoxic effects include confusion, ataxia, blurring of vision, dizziness and peripheral neuritis. A common toxic effect is red skin with orange discoloration of body fluids. Fatalities from adverse reactions have been reported. Though, the frequency of all side events is usually small and the most frequent are due to rush (2%) and GI tract (1%) [47] Rifampicin has shown no significant effects on the human fetus. It diffuses into milk and other body fluids. Contraindications: Rifampicin is contraindicated in known cases of hypersensitivity to the drug. It may be contraindicated in pregnancy (because of teratogenicity noted in animal studies and since the effects of drugs on fetus has not been established) except in the presence of a disease such as severe tuberculosis. It is contraindicated in alcoholics with severely impaired liver function and with jaundice.

Rifampicin is a potent inducer of cytochrome P-450 oxidative enzymes. Examples of well-documented, clinically significant interactions include warfarin, oral contraceptives, cyclosporine, glucocorticoids, ketoconazole, theophylline, quinidine, digitoxin, and verapamil. Recent reports have demonstrated clinically relevant interactions with protease inhibitors, zidovudine, delavirdine, itraconazole, nifedipine, midazolam or triazolam, nortriptyline, and doxycycline. [48]

Monitoring of clinical response and blood drug concentrations is essential to adjust the drug dosage during rifampicin therapy. Rifampicin also interacts with cholephils such as bilirubin and bromosulphthalein. Its pharmacokinetics are reported to be altered by ethambutol, p-aminosalicylic

acid (through its excipient component), ketoconazole, cyclosporin, clofazimine, probenecid and phenobarbital through one or other of the following mechanisms --impaired absorption of rifampicin, competition between the drug and rifampicin for hepatic uptake and altered hepatic metabolism of rifampicin. [49]

Routes of entry: Oral: This is the common route of entry. Eye: Use for ocular chlamydial infection treatment. Parenteral: Rifampicin may be given intravenously. [15] There is no information if iv rifampicin can be administered simultaneously with other drugs. The studies on ex-temporal stability are required.

Unfortunately there is no published information about specific side effects of rifampicin due to iv route of administration, it is assumed that all side effects may be similar to those that occur with prolonged infusions - inflammation and pain at the catheter insertion site, the risk of infection and thrombosis, but all these phenomena should be studied in a special study. However, a small study indicated that long-term infusions with isoniazid and rifampicin did not produce specific route -of-administration side effects. [50] There is a small study describing possibility to decrease side effects related by using iv route of administration of 2nd-line anti-TB drugs in MDR-TB patients, such as pain in the place of injection and phlebitis, by using port-catheter for intensive intravenous chemotherapy. [51]

11. Summary of available data on comparative cost and cost- effectiveness within the pharmacological class or therapeutic group.

There is no shown evidence in pharmacoeconomic convenience of i.v. rifampicin, considering following facts:

1) Low effectiveness of oral rifampicin on severe forms of tuberculosis.

2) Rare presence of i.v. rifampicin on most of the world markets, because of the absence in EML and EMLc.

According to available online data on the prices, we suppose that injectable dosage form of rifampicin can be more expensive than the oral form. Median Price for oral form of rifampicin is 0,06-0,19 usd/tab. [42] But it shouldn't be considered as an alternative drug, because oral forms cannot provide the same benefits for people affected by severe forms of tuberculosis.

IV rifampicin 600 mg powder for injections is registered on several markets, including USA, Ukraine, Russian Federation, Belarus, China, and price range is $ 8-65 per vial. Appearance of intravenous rifampicin in the list of EML and EMLc will stimulate the manufacturers to produce IV rifampicin and the concurrence will decrease the prices for the treatment course.

12. Summary of regulatory status of the medicine

I.V. Rifampicin is available in the United States, country under FDA regulation.

13. Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Rifampicin reference standards are available according to BP, IP, USP, EP.

14. References

1. WHO Model Prescribing Information: Drugs Used in Mycobacterial Diseases (1991; 44 pages)

2. Dian S, Yunivita V, Ganiem AR, Pramaesya T, Chaidir L, Wahyudi K, et al.. (2018). A double-blinded randomised placebo-controlled phase II trial to evaluate high dose rifampicin for tuberculous meningitis: a dose finding study. Antimicrobial Agents and Chemotherapy. 10.1128/AAC.01014-18.

3. Aarnoutse RE, Kibiki GS, Reither K, Semvua HH, Haraka F, Mtabho CM, et al.. (2017). Pharmacokinetics, tolerability and bacteriological response of 600, 900 and 1200 mg rifampicin daily in patients with pulmonary TB. Antimicrobial Agents and Chemotherapy. 61. AAC.01054-17. 10.1128/AAC.01054-17.

4. Yunivita V, Dian S, Ganiem AR, Hayati E, Hanggono Achmad T, Purnama Dewi A, Teulen M, Meijerhof-Jager P, van Crevel R, Aarnoutse R, Ruslami R. Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients. Int J Antimicrob Agents. 2016 Oct;48(4):415-21. doi: 10.1016/j.ijantimicag.2016.06.016. Epub 2016 Jul 26. PubMed PMID: 27526979.

5. WHO/HTM/TB/2016.16 Target Regimen Profiles for TB Treatment, Treatment of Tuberculosis: Guidelines. 4th edition Geneva: World Health Organization

6. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003 Jun 20;52(RR-11):1-77. Erratum in: MMWR Recomm Rep. 2005 Jan 7;53(51):1203.

7. Simonovska L, Trajcevska M, Mitreski V, Simonovska I. The causes of death among patients with tuberculosis; European Respiratory Journal Sep 2015, 46 (suppl 59) PA2713; DOI: 10.1183/13993003.congress-2015.PA2713

8. WHO model list of essential medicines, 2019

9. Pinheiro, Valéria G. F., Ramos, Lysiane M. A., Monteiro, Helena S. A., Barroso, Elizabeth C., Bushen, Oluma Y., Façanha, Mônica C., Peloquin, Charles A., Guerrant, Richard L., & Lima, Aldo A. M.. (2006). Intestinal permeability and malabsorption of rifampin and isoniazid in active pulmonary tuberculosis. Brazilian Journal of Infectious Diseases, 10(6), 374- 379. https://dx.doi.org/10.1590/S1413-86702006000600003\

10. Kuzhko MM, Butov DO, Hulchuk NM, Avramchuk OV, Protsyk LM, et al. (2015) Clinical Case of Using Intravenous Forms of AntiTuberculosis Drugs to Improve the Treatment Efficiency of Tuberculosis in Patients with Malabsorption Syndrome. J Pulm Respir Med 5: 269. doi:10.4172/2161- 105X.1000269

11. Frame RN, Johnson MC, Eichenhorn MS, Bower GC, Popovich J Jr. Active tuberculosis in the medical intensive care unit: a 15-year retrospective analysis. Crit Care Med. 1987 Nov;15(11):1012-4

12. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT: Mortality among patients with tuberculosis requiring intensive care:a retrospective cohort study. BMC Infect Dis 2010, 10: 54. 10.1186/1471-2334-10-54

13. Efsen AM, Panteleev AM, Grint D, Podlekareva DN, Vassilenko A, Rakhmanova A, et al. TB Meningitis in HIV-Positive Patients in Europe and Argentina: Clinical Outcome and Factors Associated with Mortality BioMed Research International Volume 2013, Article ID 373601, 9 pages http://dx.doi.org/10.1155/2013/373601

14. Metushi, I., Uetrecht, J., and Phillips, E. (2016) Mechanism of isoniazid-induced hepatotoxicity: then and now. Br J Clin Pharmacol, 81: 1030–1036. doi: 10.1111/bcp.12885.

15. https://toxnet.nlm.nih.gov/cgi- bin/sis/search2/r?dbs+hsdb:@term+@rn+13292-46-1

16. Mason PH, Sweetland AC, Fox GJ, Halovic S, Nguyen TA, Marks GB. Tuberculosis and mental health in the Asia-Pacific. Australas Psychiatry. 2016 Dec;24(6):553-555. Epub 2016 May 20. Review. PubMed PMID: 27206468; PubMed Central PMCID: PMC5332205

17. Alwood K, Keruly J, Moore-Rice K, Stanton DL, Chaulk PC, Chaisson RE. Effectiveness of supervised intermittent therapy for tuberculosis in HIV - infected patients, AIDS , 1994, vol. 8 (pg. 1103-8)

18. Berning SE, Huitt GA, Iseman MD, Peloquin CA. Malabsorption of antituberculosis medications by a patient with AIDS, N Engl J Med , 1992, vol. 327 (pg. 1817-8)

19. Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications, N Engl J Med , 1993, vol. 329 (pg. 1122-3)

20. Patel KB, Belmonte R, Crowe HM. Drug malabsorption and resistant tuberculosis in HIV -infected patients, N Engl J Med , 1995, vol. 332 (pg. 336- 7)

21. Peloquin CA, Nitta AT, Burman NJ, et al. Low antituberculosis drug absorption in patients infected with human immunodeficiency virus, Ann Pharmacother , 1996, vol. 30 (pg. 919-23)

22. Gordon SM, Horsburgh CRJr, Peloquin CA, et al. Low serum levels of oral antimycobacterial agents in patients with disseminated Mycobacterium avium complex disease, J Infect Dis , 1993, vol. 168 (pg. 1559-62)

23. Todoriko L.D., Pidverbetska O.V., Popovich M.G. Aspects of diagnosis of malabsorption syndrome in patients with tuberculosis. Conducting tactics / Medicus. – 2015. – №1. – P.69-70.

http://scimedicus.ru/d/743528/d/spisok-avtorov-medicus-(-1-(1)-yanvar).pdf

24. Todoriko L.D., Pidverbetska O.V. Clinical features of the drug susceptible, multi drug resistant and HIVassociated pulmonary tuberculosis depending on the degree of colon dysbiosis / Science and Education a New Dimension. Natural and Technical Sciences, IV (9), Issue: 83, 2016. – P. 64-67. http://seanewdim.com/published-issues.html

25. Todoriko L.D., Pidverbetska O.V. The condition of colon microbiocenosis in patients with pulmonary tuberculosis depending on the sensitivity spectrum of Mycobacterium tuberculosis and in patients with HIV/TB comorbidity / Tuberculosis, Lung Diseases, HIV infection.-2015.-№.3.-P.39-44. http://tubvil.vitapol.com.ua/svizhij_nomer.php?nid=22

26. Todoriko L.D., Pidverbetska O.V. Evaluation of the absorption ability of the small intestine in patients with lungs TB and with a different profile of drug resistance of Mycobacterium TB / Infectious diseases. - 2015.-№3.P.65-68. https://ojs.tdmu.edu.ua/index.php/inf-patol/index

27. Todoriko L.D., Pidverbetska O.V. Intestinal microbiocenosis in patients with pulmonary tuberculosis, depending on the variant of pharmacoresistance before treatment / Actual Infectology. – 2015. – № 4(9). – P. 62-65. http://www.mif-ua.com/archive/article/42083

28. Todoriko L.D., Pidverbetska O.V. Optimization etiotropic and pathogenetic treatment of patients with primary diagnosed sensitive tuberculosis in consider of the functional condition of the intestine / Tuberculosis, Lung Diseases, HIV infection.-2016.-№.2.-C.56-62. http://tubvil.vitapol.com.ua/svizhij_nomer.php?nid=25

29. Todoriko L.D., Pidverbetska O.V., Besedinska A.V. Features of the organization of nuclear chromatin of epithelial cells of the small and large intestine in patients with pulmonary tuberculosis / Reports of Morphology (Vinnytsia National Medical University named after NI Pirogov). – 2016. – T.22, №1. – 68-70.

https://www.vnmu.edu.ua/downloads/other/visnik_morf_22(1).pdf

30. Todoriko L.D., Pidverbetska O.V. Features of the functional state of the intestine in patients with pulmonary tuberculosis, depending on the sensitivity spectrum of Mycobacterium tuberculosis / Bukovinian Medical Herald Journal – 2016. – № 2 (78). – P. 166-168. https://www.bsmu.edu.ua/files/BMV/BMV-2016-20-02%2878%29/41.pdf

31. Todoriko L.D., Pidverbetska O.V., Pidverbetskiy O.Ia., Slivka V.I. Absorption activity of the small intestine in patients with TB/HIV / International scientific and practical journal " RECIPE". – 2018. – Annex 2018 (Materials I Congress of Phthisiatricians and Pulmonologists of the Republic of Belarus "Modern directions of development of respiratory medicine and phthisiology") – P. 248-250. https://elibrary.ru/title_about.asp?id=28384

32. Todoriko L.D., Pidverbetska O.V., Kuzhko M.M., Sprinsyan T.A., Yeremenchuk I.V., Semyaniv I.A. Evaluation of the effectiveness of treatment of susceptible tuberculosis with a low rate of absorption and malabsorption syndrome when administered intravenously with anti - tuberculosis drugs / International scientific and practical journal " RECIPE". – 2018. – Annex 2018 (Materials I Congress of Phthisiatricians and Pulmonologists of the Republic of Belarus "Modern directions of development of respiratory medicine and phthisiology") – P. 251-253. https://elibrary.ru/title_about.asp?id=28384

33. Todoriko L.D., Pidverbetska O.V., Yeremenchuk I.V., Semyaniv I.A. Characteristic of the functional state of the intestine at multidrug-resistant pulmonary tuberculosis / International scientific and practical journal " RECIPE". – 2018. – Annex 2018 (Materials I Congress of Phthisiatricians and Pulmonologists of the Republic of Belarus "Modern directions of development of respiratory medicine and phthisiology") – P. 260-262. https://elibrary.ru/title_about.asp?id=28384

34. M.Kuzhko et al, "Opportunities for pharmacotherapy for pulmonary tuberculosis" 2012. http://irbis-nbuv.gov.ua/cgi-bin/irbis_nbuv/cgiirbis_64.exe?I21DBN=LINK&P21DBN=UJRN&Z21ID=&S21REF=10&S21CNR=20&S21STN=1&S21FMT=ASP_meta&C21COM=S&2_S21P03=FILA=&2_S21STR=Tlkhvil_2012_4_11

35. Mbaave, Tsav & Achinge, G.I & Obekpa, S.A. (2016). Cryptic Miliary (Disseminated) Tuberculosis: A Case Report. IOSR Journal of Dental and Medical Sciences. 15. 84-86. 10.9790/0853-150758486.

36. Mert A, Arslan F, Kuyucu T, et al. Miliary tuberculosis: Epidemiologicaland clinical analysis of large-case series from moderate to low tuberculosis endemic Country. Medicine (Baltimore). 2017;96(5):e5875.

37. Lesnic E, Caraiani O, Zlepca V. Features and treatment outcome in caseous pneumonia. Eur Respir J. 2012;40(Suppl 56):P2600.

38. Bridges DA, Bedimo RG. Severe Tuberculosis Sepsis in an Immunocompetent Patient. Bridges, The American Journal of Medicine, 2006: Volume 119 , Issue 3 , e11 - e14

39. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004;351(17):1741-51.

40. New Jersey Medical School National Tuberculosis Center. Outpatient Infusion Therapy for Multidrug-Resistant Tuberculosis: A Practical Guide. 2004: (inclusive pages).

41. http://www.stoptb.org/gdf/drugsupply/catalogue.asp

42. Faisal F. Syed, Bongani M. Mayosi, A Modern Approach to Tuberculous Pericarditis, Progress in Cardiovascular Diseases, Volume 50, Issue 3, 2007, Pages 218-236, ISSN 0033-0620,

https://doi.org/10.1016/j.pcad.2007.03.002.

3 Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46.

44. Dursun Tatar, Gunes Senol, Cenk Kirakli, Ozlem Edipoglu, Pinar Cimen, Contributing factors to mortality rates of pulmonary tuberculosis in intensive care units, Journal of the Chinese Medical Association, Volume 81, Issue 7, 2018. https://doi.org/10.1016/j.jcma.2018.02.003.

45. WHO, Global tuberculosis report 2020 https://www.who.int/publications/i/item/9789240013131
46. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 UPDATE https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf
47. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med. 2003;167(11):1472-7.
48. Strayhorn VA, Baciewicz AM, Self TH. Update on rifampin drug interactions, III. Arch Intern Med. 1997;157(21):2453-8.
49. Venkatesan K. Pharmacokinetic drug interactions with rifampicin. Clin Pharmacokinet. 1992;22(1):47-65.
50. Koestner JA, Jones LK, Polk WH, Sawyers JL. Prolonged use of intravenous isoniazid and rifampin. DICP. 1989;23(1):48-50.

51. Cherenko SO, Lytvynenko NA, Reva OA, Khmel OV, Veremeenenko RA, Pogrebna MV, et al. Safety and efficiency of the port-catheter for intensive intravenous chemotherapy in patients with multi-drug resistant tuberculosis and extensively drug-resistant tuberculosis. Infusion & Chemotherapy. 2018(1):19-24.