EUROPEAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH AND MANAGEMENT STUDIES

VOLUME03 ISSUE10
DOI: https://doi.org/10.55640/eijmrms-03-10-28 Pages: 156-169

MANAGEMEND OF TUBERCULOSIS: SOME ASPECTS

Aslonov Farrukh Ismoilovich
Department Of Phthisiology And Pulmonology Bukhara State Medical Institute, Uzbekistan

ABOUT ARTICLE

Key words: RIF, INH, pyrazinamide (PZA) and ETM.

Received: 16.10.2023
Accepted: 21.10.2023
Published: 26.10.2023

Abstract: Alongside research into obtaining accurate and timely diagnostics, there is tremendous work ongoing in developing safe, efficacious, tolerable treatment regimens. The goals of treatment are not only to eradicate disease, but to prevent long-term morbidity arising from either the disease itself as an adverse effect of the drugs in use. Successful treatment of drug-sensitive TB (DS-TB) has been reported in 85% of patients. Efficacy in drug-resistant forms is lower at 57% and is likely multifactorial. To reflect this, there has been a trend towards oral drug regimens, where possible, given research highlighting patient preference and cost-effectiveness of these drugs. We need to deliver a regimen that will not only aid our global goal of TB eradication, but in a manner that reflects our patients' wishes, and in doing so, promotes their compliance.

INTRODUCTION

DS-TB tends to follow a standard 6-month regime. This comprises an intensive phase with 2 months treatment consisting of RIF, INH, pyrazinamide (PZA) and ETM, followed by a continuation phase with 4 months treatment of RIF and INH. If the isolate is susceptible to both RIF and INH, ETM can be stopped. The continuation phase should be extended to 7 months in the presence of: cavitation on the initial chest radiograph; persistent sputum growth at 2 months; or if PZA cannot be used due to monoresistance or drug side-effects. Consideration should also be given to extending this phase to 7 months in patients who are otherwise immunosuppressed, such as patients with HIV, diabetes mellitus, malignancy or medications associated with immunosuppression. Unfavorable outcomes are most

associated with high grade smear positivity (at least 3+) and dependent on the size of cavities, as well as extent of disease on chest radiographs.

Current treatment of drug-resistant TB is more complex and is summarised in table 2. Most notable is the longer duration of treatment involving combinations of drugs that are often poorly tolerated. There is also minor discordance between the two major international advisory bodies (the WHO and the joint ATS/CDC/ERS/IDSA clinical practice guideline) concerning optimum drug selection and durations. While the WHO recommends only four drugs need to be used in the intensive phase of treatment, the ATS/CDC/ERS/IDSA propose continuing to use five drugs in this phase. The ATS/CDC/ERS/IDSA have proposed this recommendation based on higher success rates in the five-drug group (93.9% versus 89.7%; adjusted odds ratio (aOR) 3.0 versus 1.2; risk difference 8% in both groups). Additionally, they suggest it is likely that one of the drugs may need to be withdrawn due to toxicity. However, given equivocal risk differences in both groups, the WHO maintain four drugs should be sufficient, providing susceptibilities are known and toxicity is unlikely. De-escalation to a continuation phase comprising three or four drugs is based on similar evidence. Traditionally, MDR-TB required treatment for a total duration of 15–21 months. Alternatively, it does allow for a shorter 9–12 month all oral regimen for patients who have not previously had more than 1 month of treatment with second-line medications, and in whom FLQ resistance has been ruled out. Additionally, patients should not have extensive disease. This shorter regimen involves 4 months of six drugs (FLQ, clofazimine (CFZ), ETH, PZA, INH (high dose)), followed by 5 months of FLQ, CFZ, ETH and PZA. BDQ is used concurrently for the first 6 months of this regimen. This conditional recommendation of low certainty evidence was proposed owing to improved success and adherence rates, when compared with shorter regimens containing injectable agents (aOR 1.9 (95% CI 1.6–2.4)). (Note, INH is used regardless of susceptibility status).

TABLE 2

Current ATS/CDC/ERS/IDSA consolidated guidelines on treating drug-resistant TB

RR-TB
As per MDR-TB
INH-resistant TB
RIF+PZA+ETM+FLQ for 6 months (can discontinue PZA after 2 months; FLQ only required in patients with extensive disease, *i.e*. cavitary or bilateral infiltrates)

MDR-TB	
First line	Levofloxacin *or* Moxifloxacin with all 4 of: Bedaquiline + Linezolid + Clofazimine# + Cycloserine#
Second line	Consider Delamanid¶2 or Pyrazinamide¶3 or Ethambutol¶1 or Amikacin *or* Streptomycin¶5
Third line	Consider ETH¶6 or Prothionamide or Imipenem-Cilastatin/Clavulante *or* Meropenem/Clavulanate¶4 or p-Aminosalicylic Acid¶7 or High Dose Isoniazid

ATS: American Thoracic Society; CDC: US Centers For Disease Control And Prevention; ERS: European Respiratory Society; IDSA: Infectious Diseases Society of America. #: in contrast, the WHO suggests only one of these drugs are required, comprising a 4-drug regimen (see text for full details): superscript numbers refer to the order in which the WHO suggests drugs be incorporated into regimes.

At present, the WHO recommends treatment for RR-TB in line with MDR-TB.

Pre-XDR- and XDR-TB are more difficult to treat, owing to varying patterns of drug resistance and advice should always be sought from national and international expert TB consortia prior to commencing treatment.

New treatment: drugs

At present, there are 16 new drugs in phase I or II clinical trials, and 22 other drugs in discovery or preclinical phases of development, as outlined in figure 1. Of those drugs undergoing clinical trial, there are 11 drugs of new chemical classes. Of the remaining drugs, TBAJ-587 and TBAJ-876 are diarylquinolines, similar to BDQ, while delpazolid, sutezolid and TBI-223 are oxazolidinones, similar to LZD and cycloserine. At the time of publication, no new drugs have reached phase III trials or been approved for market regulation since the approval of pretomanid (Pa) in 2019. A promising candidate from a new drug class is telacebec. It induces bacterial cell death by inhibiting the mycobacterial cytochrome bc1 complex responsible for ATP synthesis. A proof-of-concept trial has shown increased rates of sputum clearance, with comparable levels of adverse events to currently approved drugs. If results from ongoing clinical trials continue to reflect this, it is likely to be approved as a third new

modern drug class with anti-tuberculous activity. This would be an important achievement as many of the other drugs in development are classified similarly to existing drugs, and as such their use in additive or substitutive places for their relative counterparts will be precluded due to concerns regarding toxicity or resistance. It is also interesting to note that these drugs in development are largely oral preparations, owing to patient preference and thus potential for greater adherence and cure.

New treatment: routes of delivery

While not a novel idea, interest in inhalation routes has been re-ignited. Numerous methods of drug delivery have been shown to be effective in animals, and additional advantages include reduced dosage and systemic toxicity. However, it would likely have no benefit on extrathoracic disease, nor would it be likely to achieve adequate therapeutic serum concentrations. Similar to the use of nebulised aminoglycosides in non-Mycobacterium tuberculosis, the potential for inhalational therapies to augment TB therapy likely lies as an adjunctive therapy to oral or injectable drug regimens. To date, there has been no data published from similar trials investigating its efficacy in sputum clearance from Mtb disease.

New treatment: regimes

In a disease that has the potential to affect one quarter of the world's population, it is astounding that no advances have been made in progressing the regimen for DS-TB since the mid-20th century. At present, international consensus guidelines continue to endorse standard 6-month regimes for the majority of cases of DS-TB, with varying longer regimens requiring expert opinion for drug-resistant cases. However, much research is being done into assessing shorter regimens with the aim of improving patient adherence and reducing risk of relapse and evolution of drug resistance, as seen in table 3.

- 1) DS-TB

- A shorter 4-month regimen of rifapentine (RFP) in combination with MFX has recently been shown to be non-inferior to the current standard 6-month regimen, as determined by negative smear or culture at 12 months, with no increase in major adverse events.

- The SimpliciTB group have evaluated a 4-month regimen comprising BDQ, Pa, MFX and PZA, in place of the standard 6-month regimen. While it has been said that no drug should ever be kept in reserve, it is unlikely that this regimen will be recommended as first-line therapy for DS-TB, given the need to preserve efficacious drug options for resistant cases.

- Shorter again with a 2-month regime, the TRUNCATE-TB trial is at recruitment phase. This multi-armed approach will assess combinations of 4–5 currently approved oral anti-tuberculous medications given daily for 8 weeks, with the potential to extend to 12 weeks.

- The RIFASHORT and ReDEFINe studies are evaluating the risk–benefit ratio of higher doses of RIF in DS-TB. The evidence base for these ongoing trials has been provided by the HIRIF trial which found an increased rate of sputum clearance, with no associated increase in toxicity, in patients on higher doses of RIF than currently recommended by the WHO.

- 2) Drug-resistant TB

- a) RR-TB

- The current recommendations for RR-TB have been considered contentious for quite some time. These longer regimens likely expose patients with mono-resistance to unnecessarily long and toxic drug regimens, and also exclude the benefits of INH therapy [61]. BEAT TB is at the enrolment stage assessing the efficacy of 6 months of BDQ, LZD, delamanid (DLM), LFX and CFZ in comparison to current practices in South Africa.

- The updated STREAM2 study is evaluating a shorter regimen for RR-TB and MDR-TB in a simultaneous multi-armed approach. Their four regimens are based on: current WHO practice; the Bangladesh regime; a 40-week all oral regimen; and a 28-week oral regimen after an 8 week intense regime that also involves INH and kanamycin (Kan).

- b) MDR-TB

- Results from the NEXT trial completed in December 2020 are awaited. This group compared 6–9 months of LZD, BDQ, LFX, PZA and ETH or INH (high dose) to current standards of care.

- TB-PRACTECAL stopped early due to superior outcomes in the intervention arm, consisting of a 6-month regimen of BDQ, Pa, LZD and MFX. Full results are awaited.

- SimpliciTB are also evaluating a regimen for RR-TB/MDR-TB consisting of the same drugs as the DS-TB protocol (BDQ, PZA, MFX, Pa) but for 6 months.

- DELIBERATE are completing a phase II safety trial reviewing the safety and pharmacokinetics of combined BDQ and DLM therapy. Given the updated consensus guidelines, these drugs will often be

given together and it is essential we have an evidence base for potential harms that may arise throughout the course of treatment.

- endTB, run by Médecins Sans Frontières, are evaluating a multi-armed approach combining varying combinations of an all oral regimen for 39 weeks. Similar to the STREAM2 study, this is the only other multi-armed trial reviewing multiple combinations of novel drugs simultaneously.

- c) XDR-TB

The ZeNix trial is the only trial, at present, that is reviewing treatment regimens for patients with pre-XDR- or XDR-TB. Using BDQ, Pa and either LZD (BPaL) or placebo for a total duration of 26 weeks, their aim is to assess rates of sputum conversion. This trial is also one of the few to follow patients for a significant period post-treatment, and patients with be reviewed for 78 weeks following the end of treatment. Data from its predecessor the Nix-TB trial has shown 88% favourable outcomes at 24 months following treatment in patients with either MDR- or XDR-TB. This BPaL regime can currently be used under operational research conditions in patients with MDR-TB, in accordance with WHO guidance.

Table 3

New Drug Regimens Under Evaluation

Trial	Drugs	Purpose	Status
ReDEFINe	RIF (HD)	Assess high-dose RIF on treatment outcomes and duration in TB meningitis	Phase II
TB-PRACTECAL	BDQ, Pa, LZD, MFX, CFZ	Assess 6 months of regimen for MDR-TB	Phase III (data Analysis)
Stream stage 2	CFZ, ETM, MFX, PZA, INH, Kan, Pro, BDQ, LFX	Varying combinations at differing durations for RR-TB and MDR-TB	Phase III

Trial	Drugs	Purpose	Status
SimpliciTB	BDQ, Pa, MFX, PZA	4 months for DS-TB 6 months for MDR-TB	Phase III
Truncate-TB	BDQ, RFP, LZD, MFX	2 months for DS TB	Phase III
TBTC study 31	RFP, INH, ETM, PZA, MFX	Evaluate 4 months treatment for DS-TB	Phase III
endTB	BDQ, DLM, LZD, MFX, PZA, LFX, CFZ	47 weeks treatment with combinations of 5 drugs for MDR-TB	Phase III
RIFASHORT	RIF (HD)	Evaluate 4 months of RIF (HD)	Phase III
NEXT trial	LZD, BDQ, PZA, ETH or INH (HD)	Evaluate efficacy of ETH or INH (HD) with 6–9 months treatment for MDR-TB	Phase III (data Analysis)
ZeNix	Pa, LZD, BDQ, Pl	Evaluate 26 weeks treatment	Phase III
DELIBERATE	BDQ, DLM	Evaluate safety in MDR-TB	Phase III
BEAT TB	BDQ, DLM, LZD, LFX, CFZ	Evaluate safety and efficacy of 6 months treatment for RR-TB	Phase III

HD: high dose; RIF: rifampicin; INH: isoniazid; RFP: rifapentine; ETM: ethambutol; PZA: pyrazinamide; MFX: moxifloxacin; LFX: levofloxacin; LZD: linezolid; ETH: ethionamide; BDQ: bedaquiline; DLM: delamanid; Pa: pretomanid; CFZ: clofazamine; Kan: kanamycin; Pro: prothionamide; Pl: Placebo. #: ClinicalTrials.gov identifier. Information from.

While many of these trials demonstrate promise for an improved approach to TB treatment, it is essential that we see long-term data on their efficacy and relapse rates prior to implementing them on a global scale. The fear is that these patients may have excellent short-term results, but disease recurs soon after with the added potential for drug resistance to develop.

New treatment: adjuncts

In addition to shorter regimens, with new or re-purposed drugs, there is research into methods of modifying the host immune response to improve treatment outcomes and prevent permanent morbidity from TB disease. As previously discussed, upon infection with Mtb the host can either suppress bacillary replication into a latent state, or the host is overwhelmed and active disease develops. Both deficient and hyperinflammatory states have been associated with TB disease morbidity and mortality, suggesting that tailoring a balanced immune response is of paramount importance to survival. With evolving knowledge of the pathways and subcellular responses involved, new therapeutic targets are being developed to assist with bacillary quiescence in the so called "host directed therapy" approach. Numerous drug targets have been suggested, largely centred on modulating macrophage activity. Proposed adjunctive therapies include vitamin D, everolimus, auranofin and CC-11050, a novel anti-inflammatory compound. Preliminary results from trial data suggest none of these compounds improve rates of sputum conversion; however, patients in receipt of CC-11050 or everolimus had increased recovery of FEV1 (forced expiratory volume in 1 s) post-treatment, perhaps solidifying the role of a balanced immune response to infection.

New treatment: the future

Going forward, with a combination of new drugs, altered durations and more effective testing of response to treatment, it is likely that each patient will have a tailored approach to TB treatment. With studies like PredictTB, aiming to determine biomarkers and radiographic appearances that predict response and likelihood of relapse, we will be able to devise a drug combination and duration with greater specificity for each patient. Similar technology may even assist with developing even more efficacious drugs in early-stage clinical trials. Additionally, it is essential that any new drug or technology developed is affordable and available to all institutions, most importantly hospitals in low-resource environments, where the majority of the global TB burden persists.

Adherence

Despite ongoing research, treatment for DS-TB has remained unchanged for decades. This highly effective regimen is often poorly tolerated by patients, and "drug holidays" are frequent during treatment. This, of course, increases the likelihood of relapse and evolution of drug resistance. Moreover, patients with resistant TB have to endure longer regimens with their own associated side-effects. While awaiting the development and approval of less toxic regimens, there are a number of measures we can take to ameliorate adverse effects of treatment and promote patient adherence. It has

been shown that comprehensive patient-centred approaches, involving nutritional, financial and psychological support, have higher rates of completion. In addition, patients with increased contact with healthcare workers tended to have lower drop-out rates during treatment. The evidence base for this is provided by systematic reviews of mostly observational case studies and case cohorts, and as such randomised research in this area is required to determine a formal link.

Directly observed therapy

Directly observed therapy (DOT) has been a standard of care in TB treatment for several years. The premise is that patients are more likely to comply if medication ingestion is witnessed multiple times per week. Current recommendations are that it should be implemented in MDR- or XDR-TB cases, or for patients with complex or vulnerable care needs, such as homelessness, comorbid psychiatric illness or addiction. There have been conflicting results from systematic reviews on the efficacy of DOT. What is known, is that community-based DOT appears to be the most effective strategy, as it is less disruptive for patients and thus their adherence is more likely to be maintained. In recent years, attention has switched towards the use of smartphone technology. Video observed therapy (VOT) has been suggested as an even less disruptive form of monitoring adherence. Patients can either upload videos of medication ingestion to a secure platform to be watched at a later date, or it can be taken while on a live feed with their healthcare team. VOT has been shown to have a higher uptake rate and patient preference rating. While plausible that this will improve adherence, and thus relapse should be less likely, this study was not sufficiently powered to assess this, nor did it follow up on relapse rates at an appropriate interval. A real-world efficacy and cost-effectiveness study is ongoing in a tertiary hospital in Ireland at present.

Prophylaxis

Undoubtedly, a burden of TB infection will persist for years to come. However, we have a chance to prevent many of these patients from progressing to active disease. Screening for TB infection in groups at high risk of progressing to TB disease remains a cost-effective and essential component to the global initiative. Screening via either of the endorsed interferon-γ release assays (QuantiFERON-TB Gold In-Tube and T-SPOT.TB) or traditional tuberculin skin testing is recommended in certain populations. The WHO has advised that clinical judgement is paramount in interpreting these tests, and cautions that a higher rate of false negatives occurs in the most vulnerable populations. Another essential component of the sustainable development goals is robust public health policy to assist in contact tracing of index

cases and early treatment of contacts. In addition, prior to any prophylactic treatment being commenced, it is essential that due caution is taken to rule out the presence of active TB disease.

Currently the WHO advocates for treatment with 4 months of RIF or 6–9 months of INH in cases where the index case is known to be drug sensitive. A 3-month combination of RIF and INH is also approved, although rarely used due to potential toxicity. Additionally, weekly INH and RFP for 3 months has been shown to demonstrate equal efficacy and toxicity in comparison to 6 months of INH therapy, while higher levels of adherence were noted in the INH/RFP arm. Moreover, a 1-month regimen of RFP/INH therapy was non-inferior to 9 months INH monotherapy in preventing TB in HIV-infected patients. However, this regimen has yet to be endorsed by major international consortia.

The recommendations for TB contacts of DS-TB cases who demonstrate evidence of TB infection are as per those above. For contacts of MDR-TB cases, the current recommendation is for 6–12 months treatment with a FLQ with or without a second drug. If a FLQ cannot be used due to resistance in the index case, treatment with ETM and PZA is to be considered. Regardless of the regimen in use, it is vital that strict adherence is maintained to ensure efficacy and prevent resistance.

At present, the decision to treat is based on the potential for progression to active disease based on similar case profiles. Going forward, we could vastly improve the cost efficacy of this intervention by being able to determine exactly which patients were going to progress to active TB disease or not. It had been hoped the answer would lie in serum transcriptional biomarkers and host response-based gene signatures. Recently, a four-protein biomarker panel has shown 67.3% sensitivity and 96.3% specificity at determining active from latent TB. This subclinical phase of TB disease can be difficult to interpret due to its lower inflammatory profile and person specific confounding factors that influence our immune response. Recent results from transcriptomic studies have been disappointing overall, but may potentially suggest a role for these panels in symptomatic patients with known TB infection and their risk of progression to TB disease in an imminent 6-month period.

Vaccination

Given the current prevalence of TB infection, with the associated lifetime risk of progressing to active disease, it is paramount that we protect future generations from this burden by halting transmission entirely. With greater understanding of the cellular processes involved in Mtb susceptibility and pathogenesis, scientists have been able to identify various potential targets with a role in vaccination. Central to this is the cellular immune response, with a need to upregulate T-helper cell (Th)1, and downregulate Th2 and regulatory T-cell responses. It appears that Mtb has also recognised the need to

adapt to this hypo-inflammatory phenotype with more modern strains displaying shorter latency and higher virulence than previously seen.

The only worldwide approved vaccine against TB remains bacillus Calmette–Guérin (BCG), effectively reducing the risk of severe childhood disease from TB, with an 85% reduction in TB meningitis and miliary TB in those <10 years of age [96]. It has also been noted that infants innoculated with BCG have increased survival and lower rates of other childhood infections. This observation is likely secondary to BCG's ability to prime innate immunity through epigenetic modification of innate immune cells.

Vaccination can be categorised into preventive pre-exposure, preventive post-exposure or therapeutic. Vaccines can alternatively be classified according to their biochemical forms: live attenuated, inactivated, protein subunit or recombinant. With each of these forms, the aim is to target various cells or subcellular components of TB pathogenesis.

MTBVAC, a pre-exposure live attenuated vaccine, has shown promising results from preclinical trials with a higher protection against TB than BCG. This live vaccine is based on a genetically modified mutant Mtb strain containing deletions in transcription factors important for Mtb growth in macrophages and subsequent virulence.

VPM1002, another live recombinant BCG vaccine, is undergoing phase III studies at present to evaluate its efficacy at not only preventing infection, but in preventing active disease in those already affected. This vaccine can modify T-cell immune response and enhance Th1 immunity, important in TB disease pathogenesis.

Another promising post-exposure candidate is M72/AS01E, a subunit vaccine, that prevents pulmonary TB in adults already infected with Mtb in 54% of patients, and thus could be a potentially life-saving intervention for one quarter of the world's population. Also known as Mtb72F this vaccine comprises two immunogenic proteins that promote T-cell proliferation and interferon-γ release.

Further randomised control trials are warranted in a timely manner if the END TB strategy is to be achieved.

CONCLUSION

The future is bright for TB treatment. Never before has there been such a global effort to develop new technologies and treatment for TB patients. Combining these advancements, it is possible that we will base each patient's treatment on their own protein biosignatures in conjunction with the genomic

expression of mutations in the Mtb strain they have been affected with. If we are to achieve our goal of global eradication of TB, it is essential that we continue to collaborate and share our expertise on an international scale to ensure each patient gets the appropriate treatment and support to overcome their TB diagnosis without significant morbidity.

REFERENCES

1. Kh, Usmonov I. "Clinical Course and Modern Diagnosis of Resistant Forms of Pulmonary Tuberculosis." American journal of social and humanitarian research 3.2 (2022): 250-260.
2. Khaydarovich, Usmonov Isomiddin, and Shukurov Umrzoq Zarifboevich. "CHALLENGES OF DIAGNOSTICS AND FEATURES OF TREATMENT FOR LUNG TUBERCULOSIS IN HIV INFECTED PATIENTS." EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE 2.2 (2022): 92-97.
3. Aslonov, F. I., S. A. Rustamova, and K. M. Raxmonova. "Immunopatological aspects in patients with first detected pulmonary tuberculosis." World Bulletin of Public Health 4 (2021): 91-95.
4. Ismoilovich, Aslonov Farrukh. "Tuberculosis Diagnostics with Modern Solutions (Literature Review)." Central Asian Journal of Medical and Natural Science 3.3 (2022): 377-383.
5. Ulugbek o'gli A. M. Factors Predicting Mortality in Pulmonary Tuberculosis //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 3. – С. 362-367.
6. Ulugbek o'gli A. M. Test for Procalcitonin as a Way to Predict Patients with Respiratory Tuberculosis //European Multidisciplinary Journal of Modern Science. – 2022. – Т. 4. – С. 486-491.
7. Ulugbekugli A. M. CLINICAL ASPECTS OF TUBERCULOSIS DISEASE //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 12. – С. 73-80.
8. Муаззамов Б. Р., Жумаев М. Ф. О преподавании фтизиатрии на лечебном и медико-педагогическом факультетах //Материалы VIII Съезда фтизиатров и пульмонологов Узбекистана. Тошкент. – 2018. – С. 109-110.
9. Муаззамов Б. Р., Муаззамов Б. Б., Медведева Н. В. ПРИМЕНЕНИЕ ИНТЕРАКТИВНЫХ ПЕДАГОГИЧЕСКИХ МЕТОДОВ ПРЕПОДАВАНИЯ ПРЕДМЕТА" ФТИЗИАТРИЯ" НА ПРИМЕРЕ ТЕМЫ" ДЕСТРУКТИВНЫЕ ФОРМЫ ТУБЕРКУЛЁЗА ЛЁГКИХ" //Новый день в медицине. – 2019. – №. 3. – С. 45-50.
10. Erkinova, Nigora. "OBSERVATION OF ALBUMINURIA IN CHRONIC HEART FAILURE AND SOME OF ITS CLINICAL FEATURES." Galaxy International Interdisciplinary Research Journal 9.05 (2021): 442-446.

11. Nigora, Erkinova, and Xuddieva Nargiza. "Observations, clinical features of albuminuria with renal changes in chronic heart failure." Academicia Globe: Inderscience Research 2.5 (2021): 1-5.

12. Erkinovna, Erkinova Nigora, and Olimova Aziza Ulugbekovna. "THE COURSE OF COMORBID CONDITIONS IN DIFFERENT FUNCTIONAL CLASSES OF CHRONIC HEART FAILURE." INTERNATIONAL CONFERENCE ON MULTIDISCIPLINARY RESEARCH AND INNOVATIVE TECHNOLOGIES. Vol. 1. 2021.

13. Алимова Г. С. Массовый Скрининг Для Выявления Туберкулезной Инфекции У Детей В Возрасте От 2 До 8 Лет //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 3. – С. 368-376.

14. Salimovna A. G. Diagnosis of Tuberculosis Infection Activity by ELISA and Transcription Analysis Methods //European Multidisciplinary Journal of Modern Science. – 2022. – Т. 4. – С. 492-497.

15. Alimova G. DETECTION OF ADOLESCENT TUBERCULOSIS IN THE REGION OF BUKHARA WITH THE HELP OF THE DRUG" DIASKINTEST" //Eurasian Journal of Medical and Natural Sciences. – 2022. – Т. 2. – №. 10. – С. 46-51.

16. Рахмонова К. М. Разработка Методов Ранней Диагностики, Лечения И Профилактики Хронической Дыхательной Недостаточности При Туберкулёзе Легких (Обзорная Литературы) //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 3. – С. 262-272.

17. Рахмонова К. М. Туберкулез Легких И Сопутствующие Заболевания //Central Asian Journal of Medical and Natural Science. – 2021. – Т. 2. – №. 6. – С. 137-144.

18. Mizrobovna R. K. Accompanying Diseases of the Respiratory System Pulmonary Tuberculosis //European Multidisciplinary Journal of Modern Science. – 2022. – Т. 4. – С. 244-250.

19. Muzrobovna R. K. Diagnosis and Treatment Patients with Pulmonary Tuberculosis with Concomitant Bronchoobstructive Syndrome //Research Journal of Trauma and Disability Studies. – 2022. – Т. 1. – №. 10. – С. 109-118.

20. Rakhmonova K. TUBERCULOSIS AND IRON-CONTAINING CHEMOTHERAPEUTIC DRUGS //Eurasian Journal of Medical and Natural Sciences. – 2022. – Т. 2. – №. 10. – С. 40-45.

21. Жумаев М. Ф. СЛОЖНОСТИ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ЛЕКАРСТВЕННО-УСТОЙЧИВЫХ ФОРМ ТУБЕРКУЛЁЗА ЛЕГКИХ //Вопросы науки и образования. – 2021. – №. 15 (140). – С. 21-27.

22. Fatullayevich J. M. BIOLOGICAL CHARACTERISTICS OF THE CAUSATIVE AGENT OF TUBERCULOSIS IN PATIENTS WITH PULMONARY TUBERCULOSIS //World Bulletin of Public Health. – 2021. – Т. 5. – С. 27-32.

23. Жумаев М. Ф. ДИАГНОСТИКА ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ ПРИ ТУБЕРКУЛЕЗЕ ЛЕГКИХ У ПАЦИЕНТОВ МОЛОДОГО ВОЗРАСТА И ПРИЧИНЫ ЕЕ ФОРМИРОВАНИЯ //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 10. – С. 358-362.

24. Жумаев М. Ф. ХАРАКТЕРИСТИКА И НЕДОСТАТКИ КЛИНИЧЕСКОЙ И МЕДИЦИНСКОЙ ДИАГНОСТИКИ ТУБЕРКУЛЕЗА ЛЕГКИХ //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 10. – С. 367-372.

25. Рустамова С. А. и др. Изучение причин и факторов, способствующих развитию рецидивов туберкулеза органов дыхания //Медицинский альянс. – 2015. – №. 1. – С. 115-115.

26. Рустамова С. А. и др. Спектр лекарственной устойчивости и эффективность лечения впервые выявленных больных туберкулезом легких //Медицинский альянс. – 2015. – №. 1. – С. 116-116.

27. Мухамедов К., Джурабаева М., Рустамова С. Частота встречаемости вирусных гепатитов среди впервые выявленных больных туберкулезом легких //Журнал проблемы биологии и медицины. – 2014. – №. 3 (79). – С. 132-133.

28. Davlatovna Y. T. MAIN DIRECTIONS OF TUBERCULOSIS RESEARCH ON PREVENTION, DIAGNOSIS AND TREATMENT //Web of Scientist: International Scientific Research Journal. – 2022. – Т. 3. – №. 10. – С. 389-396.

29. Yitmasova T. BASIC RESEARCH METHODS IN TUBERCULOSIS PREVENTION AND TREATMENT //Theoretical aspects in the formation of pedagogical sciences. – 2022. – Т. 1. – №. 5. – С. 55-56.