International Journal of Infectious Diseases 92S (2020) S10–S14

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Rehabilitation, optimized nutritional care, and boosting host internal milieu to improve long-term treatment outcomes in tuberculosis patients

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ARTICLE INFO

Article history:
Received 8 January 2020
Received in revised form 16 January 2020
Accepted 16 January 2020

Keywords:
Tuberculosis
Pulmonary rehabilitation
Disease-related malnutrition
Immune response

ABSTRACT

Background: The holistic management of tuberculosis (TB) patients can improve life expectancy and lost organ function.
Rehabilitation: Chronic sequelae are very common among patients who survive TB, which can lead to a further decline in lung function. There is still no guidance for 'cured' patients with impaired lung function who need pulmonary rehabilitation. Additional tests for evaluation should be given after the end of treatment, as recent studies have shown the good effect of pulmonary rehabilitation for TB patients.
Optimized nutritional care: Malnutrition is very common among TB patients and is related to malabsorption. The latter can cause lower drug exposure, which may result in treatment failure, increasing the risk of death, and can lead to acquired drug resistance. Malnutrition should be assessed according to the Global Leadership Initiative on Malnutrition (GLIM) criteria and the diagnosis should lead to an individualized treatment plan, including sufficient proteins and preferably in combination with adequate training.
Protective immune responses: Under normal circumstances, most immune cells use a glucose-based mechanism to generate energy. Therefore the patient's nutritional status is a key factor in shaping immune responses. Disease-related malnutrition leads to proteolysis and lipolysis. In the end, the identification of individuals who will benefit from immune-modulatory strategies may lead to clinically relevant markers.

Introduction

Tuberculosis (TB) remains an important cause of mortality globally; however, very little is said of the hundreds of millions of patients who survive the disease. Chronic sequelae are very common, which can range from reduced lung function and post-TB bronchiectasis to aspergilloma and non-tuberculous infections, all of which can further impact lung function. We are only now gaining a better insight into TB as a systemic inflammatory process and understanding that patients are more likely to suffer from vascular events after TB cure. Our ex-TB patients can be expected to be more fragile (Choi et al., 2017a) and are still likely to die 4 years

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https://doi.org/10.1016/j.ijid.2020.01.029

earlier (Hoger et al., 2014) even though they are cured. The question is, why is this the case and what can be done about it?

The following article discusses the state of the art on the holistic management of TB patients aimed at recuperating lost organ function and raising post-TB life-expectancy, as well as topics for future research in the field. In particular the review is focused on (1) the functional evaluation of TB patients at the end of treatment and rehabilitation of sequelae; (2) optimization of nutritional care, and (3) new insights into the protective immune response.

Methods

A non-systematic review of the literature was conducted by the members of the writing committee, so as to include useful core references that may help the reader better understand the topics covered. The following keywords were used, without any time limitation: 'tuberculosis', 'functional evaluation', 'pulmonary rehabilitation', 'nutrition', 'protective immune response'. MEDLINE was used as the search engine, focusing on the English-language literature only.

Rehabilitation for TB patients

Functional evaluation of patients and pulmonary rehabilitation

TB control programmes have prioritized early diagnosis and effective treatment of infectious cases to ensure rapid cure of individual patients and interruption of the transmission chain. Given most of the global TB burden is localized in countries with limited economic resources, the importance of investigating the functional status of the patients declared 'cured' to assess potential abnormalities and candidates for pulmonary rehabilitation has not gained much attention (Amaral et al., 2015; Muñoz-Torrico et al., 2016; Spruit et al., 2013).

With a main focus on chronic obstructive pulmonary disease (COPD), the American Thoracic Society/European Respiratory Society (ATS/ERS) rehabilitation guidelines indicate that rehabilitation is an effective intervention in chronic respiratory diseases, although TB is not individually mentioned. Recent evidence has shown that obstructive and/or restrictive functional sequelae may occur, potentially affecting quality of life (QoL) (Amaral et al., 2015; Muñoz-Torrico et al., 2016). Currently, no guidance on specific indications and procedures regarding the study and rehabilitation of TB sequelae is available (Amaral et al., 2015; Muñoz-Torrico et al., 2016), although TB rehabilitation was recently recommended in the ATS/ERS/Infectious Disease Society of America (IDSA)/Centers for Disease Control and Prevention (CDC) multidrug-resistant (MDR)-TB guidelines (Nahid et al., 2019).

The preliminary data available suggest that pulmonary rehabilitation is effective in patients with a previous history of TB and with impaired lung function. As more and more countries are potentially able to financially support rehabilitation for patients with post-TB sequelae, well-designed prospective studies are necessary to identify the individuals needing further assessment and to clarify which rehabilitation models can be implemented to ensure a functional recovery (Visca et al., 2019).

The evidence available on lung function impairment

A few studies have investigated mechanical lung function in TB patients. Already in 1961, Hallet and Martin described a 'diffuse obstructive pulmonary syndrome' among TB patients admitted to sanatoria (Hallett and Martin, 1961). Willcox and Ferguson (1989) identified airway obstruction in 68% of patients completing anti-TB treatment, with an inverse relationship between the extent of chest radiography lesions and forced expiratory volume in the first second (FEV_1). Similarly, in South Africa, TB was found to be responsible for lung function impairment (Hnizdo et al., 2000). In a large population-based study involving 14 050 participants from 18 countries, a history of previous anti-TB treatment was associated with both airflow obstruction and spirometry restriction, and it was concluded that TB is a major cause of COPD in countries with a high TB prevalence (Amaral et al., 2015).

Worldwide, several studies have identified TB (treatment) as a positive predictor for loss of lung function. The conclusions of a South Korean study conducted between 2008 and 2012 recommended coupling regular lung function testing and smoking cessation as preventive measures for chronic airway obstruction (Jung et al., 2015). A study conducted in India in 2015 identified obstructive, restrictive, and mixed lung impairment disorders in TB patients after completing their treatment (Sailaja and Nagasreedhar, 2015). In China, treated TB was identified as an independent risk factor for airflow obstruction (Lam et al., 2010). In Papua New Guinea, effective management (early diagnosis and adequate treatment) of MDR-TB patients was considered essential to prevent post-treatment sequelae (Ralph et al., 2013).

Furthermore, a multicentre population-based study in Latin America involving over 5500 patients in five cities revealed that (self-reported) history of previous anti-TB treatment was significantly associated with airflow obstruction (Menezes et al., 2007). In Mexico, 70 patients cured of pulmonary TB were investigated, and frequent obstructive abnormalities were found, with impaired QoL (de la Mora et al., 2015). Last, in Texas, United States, pulmonary function was evaluated twice, after 20 weeks and at the end of anti-TB treatment, and TB treatment was identified as an independent risk factor for COPD, both in smokers and non-smokers (Vecino et al., 2011).

Therefore, it was recently suggested that lung function be assessed by performing spirometry, plethysmography, DLCO (diffusion for carbon oxide), arterial blood gas analyses, and evaluating the capacity to perform exercise via the 6-min walk test (6MWT). It is possible to describe the lesions with chest radiography and computed tomography before and after treatment. Clearly, the clinical assessment of infectious cases implies adequate infection control measures are in place (Migliori et al., 2019).

The evidence available on pulmonary rehabilitation

TB is clearly mentioned among the conditions for which pulmonary rehabilitation is useful according to the ATS/ERS guidelines and the South African COPD management guidelines (Spruit et al., 2013). In a recent study (Visca et al., 2019), pulmonary rehabilitation was effective in patients with a previous history of anti-TB treatment. Patients with impaired lung function reported a significant improvement in 6MWT, Borg dyspnoea and fatigue scores, FEV_1, forced vital capacity (FVC), mean arterial oxygen partial pressure (PaO_2), and median arterial blood oxygen saturation (SaO_2) (Visca et al., 2019).

In a recent editorial and in studies conducted in Benin, Zimbabwe, and Uganda (Chin et al., 2019; Fiogbe et al., 2019; Harries and Chakaya, 2019; Jones et al., 2017), the issue of the feasibility of post-treatment functional assessment of TB patients and subsequent pulmonary rehabilitation was discussed, with a focus on the perspective of low-income countries. In Uganda, a pulmonary rehabilitation package supervised by physiotherapists and requiring minimum equipment initiated at the health facility level, with aerobic and resistance exercises later managed at home, was demonstrated to be feasible and associated with clinically important improvements in QoL, exercise capacity, and respiratory outcomes (Jones et al., 2017).

A recent review (Hoger et al., 2014) recommended that future evaluation of post-treatment sequelae include the following (Figure 1): detailed information on patient characteristics (age, sex, ethnicity, etc.), TB disease (history of previous treatment, bacteriological status and pattern of drug resistance, previous drugs and regimens with adverse events), and pathophysiological status (spirometry with bronchodilator response), assessment of lung volumes (plethysmography), DLCO, arterial blood gases analysis, 6MWT, radiological evaluation, QoL evaluation, rationale and the features of the rehabilitation plan (with clear pre-/post-test comparisons), and a cost evaluation. Furthermore, studies should quantify the proportion of patients needing rehabilitation among those completing treatment. This will allow the need for pulmonary rehabilitation to be estimated and adequately planned at the programmatic level.

Optimized nutritional care for TB patients

The history of nutritional care

Nutritional care has been an important component of TB treatment throughout the history of European civilization. Lacking adequate drugs, Hippocrates' TB treatment consisted of resting, praying, drinking milk, exercise, and avoiding extreme weather conditions (Madkour et al., 2004). At the end of the nineteenth century, in the first sanatorium for TB patients, a more specific nutritional regimen was implemented in TB treatment. This diet was "a mix of meat with plenty of vegetables" (Kinghorn, 1921). Furthermore, to treat symptoms like night sweats, cognac was used (Kinghorn, 1921). In the first randomized trial testing the potential of streptomycin injections, the control standard of care consisted of nutrition and bed rest (Streptomycin in Tuberculosis Trials Committee, 1948). In 2013, the World Health Organization (WHO) published the first guidelines on nutritional care and support specifically for patients with TB. In these guidelines, the WHO stressed that all patients with active TB are entitled to individualized nutritional assessment and management, including counselling and therapy (World Health Organization, 2013).

Malnutrition and its implications for TB

Malnutrition is defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" (Cederholm et al., 2017). In general, malnutrition is reported to have a huge impact on patient outcomes and healthcare costs (Muscaritoli et al., 2017). Disease-related malnutrition is characterized by a loss of fat-free mass; therefore, normal weight, overweight, and obese patients with TB can be malnourished (Paton et al., 2004). This implies a decline in muscle function, which leads to dependency and less participation in society for the patient. Regaining physical function shortens the time needed for recovery and enables patients with TB to resume work (Cederholm et al., 2017; Paton et al., 2004). The prevalence of malnutrition in patients with TB is calculated to be 70%, and in this population, malnutrition is associated with a two-fold higher risk of dying from TB (Bhargava et al., 2013).

Malnutrition is considered an important potentially reversible risk factor for TB treatment failure (Choi et al., 2017b). It is hypothesized that pharmacokinetic variability, resulting from changes in malabsorption (Montalto et al., 2008), can influence efficacy. Patients with TB may suffer from malabsorption because of malnutrition, which can be increased by possible comorbidities such as diabetes and HIV/AIDS. Subsequently, decreased absorption of anti-TB drugs is likely to result in low drug exposure. This may lead to unfavourable outcomes by treatment failure and the development of drug resistance (Ter Beek et al., 2019).

Nutritional assessment, therapy, and monitoring

Malnutrition is not disease-specific but is a 'nutrition disorder' (Cederholm et al., 2017). As low body mass index (BMI) is a hallmark of chronic malnutrition that involves the loss of both fat and muscle tissue, a BMI < 18.5 kg/m^2 may be used as a measure for general public health purposes (Cederholm et al., 2015). However, in clinical practice, using BMI exclusively is of less relevance for nutritional assessment, since in disease-related malnutrition,

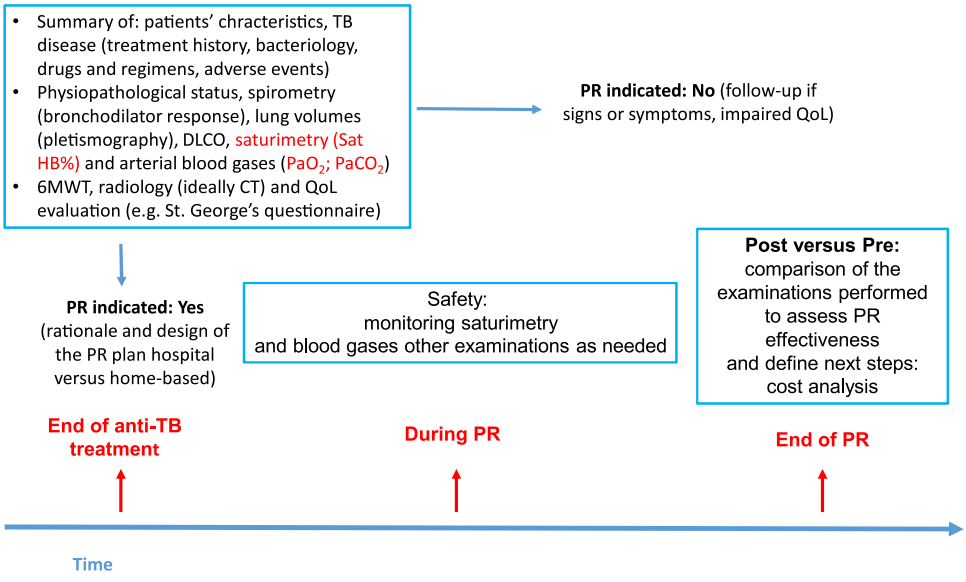

Figure 1. Summary of the core interventions at the end of anti-tuberculosis treatment and during pulmonary rehabilitation.
DLCO: diffusing capacity of the lung for carbon monoxide; Sat HB%: haemoglobin saturation as a percentage; PaO_2/$PaCO_2$: arterial blood tension of oxygen and carbon dioxide; 6MWT: 6-min walking test; CT: computed tomography; QoL: quality of life; PR: pulmonary rehabilitation.

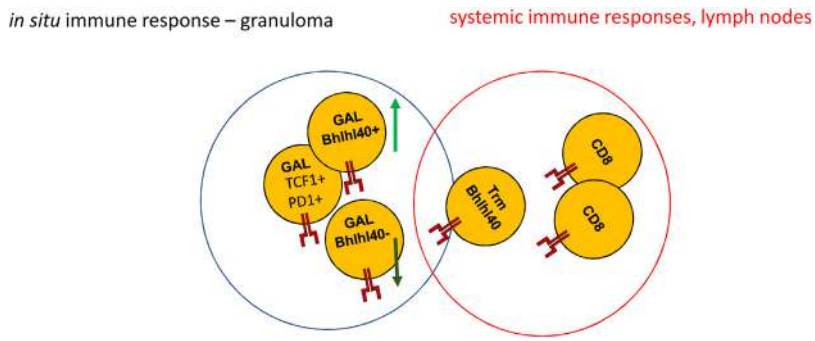

Figure 2. Immune responses in *Mycobacterium tuberculosis* infection. Tissue resident T-cells (Trm) and tumour infiltrating T-cells (TIL) exhibit increased Bhlhle40 expression; however, this is not the case for peripheral (CD8+) T-cells. GAL (granuloma-associated lymphocytes; Tully et al; 2005) correspond to TIL. Increased Bhlhle40 is associated with increased immune effector functions, increased 'mitochondrial fitness', and increased competence to contain pathogens or transformed cells (light green arrow). In contrast, decreased Bhlhe40 expression is linked with loss of immune competence (dark green arrow). Immune cells may be recruited into the granuloma via Trm resources, from the peripheral circulation, or from lymph nodes. TCF1+ PD1+ T-cells have stem-like properties and are crucial in long-term immune memory. Antigen-specific CD8+ T-cells are vital for immune surveillance, but may also be responsible for mediating cachexia.

muscle mass is mainly lost (Cederholm et al., 2015). A gold standard for malnutrition is not available, which complicates consensus on how nutritional assessment and its validation should be conducted. However, in 2018, consensus diagnostic criteria for malnutrition were published by ESPEN and the American Society for Parenteral and Enteral Nutrition (ASPEN) to accommodate uniformity in nutritional assessment, i.e. the 'GLIM criteria' (Global Leadership Initiative on Malnutrition) (Cederholm et al., 2019). These criteria are both phenotypic (weight loss, low BMI, reduced muscle mass) and aetiological (reduced food intake or assimilation, disease burden/inflammatory condition), and are preceded by validated screening for malnutrition risk (Cederholm et al., 2019).

After diagnosing malnutrition, an individualized treatment plan needs to be developed. This tailored treatment plan needs to be based on sufficient proteins (and distribution) and energy from either regular foods or medical nutritional supplements if necessary, and preferably in combination with training (Ockenga et al., 2006). The nutritional counselling and measurements that are performed to assess malnutrition should be repeated regularly during the treatment and (pulmonary) rehabilitation period, to allow adjustment of the nutritional treatment plan if necessary.

New insights from protective immune responses—cross-fertilizing concepts for anti-MTB immune surveillance

New insights from cancer research and biological therapy are guiding innovative immunological therapies targeted against defined molecular targets. A novel pathway has been suggested on how disease-related malnutrition is mediated, and is a common finding in TB patients. Nutritional status is a key factor in shaping immune responses. Under normal circumstances, most immune cells use a glucose-based mechanism to generate energy. In nutrient-deficient states, alternative sources are used to generate energy, such as proteins and fatty acids. Baazim et al. showed that infection-induced cachexia is not only mediated by tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 leading to proteolysis and lipolysis, but also by antigen-specific CD8+ T-cells that mediate cachexia by adipose tissue remodelling (Baazim et al., 2019) (Figure 2). Furthermore, the containment of tissue infections requires the involvement of tissue resident immune cells (Trm cells). These cells are enriched in the lung and are thought to mediate an important line of defence against invading pathogens (Behr et al., 2018). Bhlh40 is a key factor mediating containment of infectious pathogens (or transformed cells) (Li et al., 2019). Mice with reduced Bhlhle40 cells exhibit reduced survival in influenza-positive animals; increased Bhlhle40 expression results in increased interferon-gamma production in the Th1 compartment. These may be promising clinically relevant markers to identify individuals who may benefit from immune-modulatory strategies targeting the biological pathways associated with long-term protective immune responses.

Conclusions

In this review on the holistic approach to TB patients, we have discussed the recent evidence on the importance of evaluating functional status at the completion of treatment in order to identify candidates for pulmonary rehabilitation. We have shown that pulmonary rehabilitation is effective in improving functional parameters, the capacity to perform exercise (walking test), and quality of life. We have described the recent evidence and implications at the immunological level, identifying priorities for future research. We have also discussed the damage produced by malnutrition and the importance of assessing the nutritional status. The importance of addressing malnutrition correctly and in a timely fashion is essential in reducing morbidity and mortality.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Approval was not required.

Conflict of interest

No competing interest declared.

Acknowledgements

This article is part of the activities of the Global Tuberculosis Network (GTN; Committees on TB Treatment, Working Group on Pulmonary Rehabilitation, and Global TB Consilium) and of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, ITA-80, 2017-2020-GBM/RC/LDA. This article is part of a supplement entitled *Commemorating World Tuberculosis Day March 24th, 2020: "IT'S TIME TO FIND, TREAT ALL and END TUBERCULOSIS!"* published with support from an unrestricted educational grant from QIAGEN Sciences Inc.

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