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Post tuberculosis treatment infectious complications

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ABSTRACT

Following greater attention and follow-up of patients with treated pulmonary tuberculosis (TB), it has emerged that infections are more likely to occur in this cohort of patients. This comes as no surprise, as pulmonary TB is a destructive process that leads to cicatrization, alteration of parenchyma, bronchiectasis, and scarring of the lung, with reduction of lung volumes and an impact on pulmonary function. In addition to relapse and re-infection with TB, other pathogens are increasingly recognized in post-TB patients. This paper serves as a summary and guide on how to approach the post-TB patient with new signs and symptoms of pulmonary infection in order to ensure optimal management and rehabilitation.

Introduction and approach

Patients with pulmonary tuberculosis (TB), even after cure, may develop further respiratory infections and lung disease, which may become chronic, leading to greater morbidity and mortality (Hnizdo et al., 2000). Exacerbations of chronic obstructive pulmonary disease (COPD), bronchiectasis, and pneumonia are more frequent after pulmonary TB (Amaral et al., 2015; Byrne et al., 2015). Lung aging is accelerated, especially in the presence of smoking and atmospheric pollution (Glaser et al., 2015; van Zyl Smit et al., 2010). Colonization and infection with non-tuberculous mycobacteria (NTM) and *Aspergillus fumigatus* are common in individuals with a degree of pre-existing lung destruction (Brode et al., 2014; Pasqualotto and Denning, 2008). In addition to TB recurrence or reinfection, all of these conditions need to be considered in the differential diagnosis when patients present with symptoms following the treatment of pulmonary TB and/or any evidence of lung function deterioration or TB sequelae is noticed.

Post-TB infections may present with similar clinical features to pulmonary TB, with haemoptysis being a common manifestation. The authors recommend taking a chest X-ray at the end of TB treatment, as this is useful for future comparison. The presence of cavitary disease may prompt the clinician to consider baseline *Aspergillus* serology. Vaccination for influenza virus may be useful in reducing further infectious insults and inflammation (Oei and Nishiura, 2012; Noymer, 2009). Six-monthly respiratory clinic follow-up in the 2 years after TB treatment may be useful in the monitoring and management of possible COPD and bronchiectasis in a subset of patients with chronic lung disease, who might need pulmonary rehabilitation. Clinicians should also be aware of the possibility, and associated higher mortality, of NTM–*Aspergillus* co-infection (Jhun et al., 2017; Naito et al., 2018).

Chronic pulmonary aspergillosis: clinical picture and management

Chronic pulmonary aspergillosis (CPA) encompasses a spectrum of disease patterns, often with considerable overlap. The major subtypes of CPA include chronic cavitary aspergillosis (CCA), chronic fibrosing aspergillosis (CFA), aspergilloma, and *Aspergillus*

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nodules. *A. fumigatus* is the causative species, but *Aspergillus niger* and *Aspergillus flavus* infections have also been reported (Pasqualotto and Denning, 2008; Severo et al., 1997). It has been estimated that patients with residual pulmonary cavities of ≥2 cm after TB treatment have a 20% chance of developing aspergillomas (British Thoracic and Tuberculosis Association, 1970). Overall estimates of the mortality rate in CPA where treatment is available range from 20–33% in the short-term to 33–80% over a 5-year period (Camuset et al., 2007; Jewkes et al., 1983; Lowes et al., 2017; Ohba et al., 2012).

Clinical features of CPA are usually non-specific and indolent in onset. Common symptoms include weight loss, chronic productive cough, fatigue, dyspnoea, and haemoptysis (Schweer et al., 2014). A simple aspergilloma without concurrent CCA/CFA often causes few or no symptoms.

Chest imaging remains an important diagnostic modality. A chest X-ray or computed tomography (CT) scan can reveal one or more cavities, typically within the upper lobes, of variable size, with or without the presence of pleural thickening and fibrosis (Desai et al., 2015). Cavities can be thin- or thick-walled, and may or may not contain fungal balls. A simple aspergilloma is usually within a single cavity, with limited inflammation, pleural thickening, and fibrosis (Denning et al., 2003).

The mainstay for diagnosis is the detection of *Aspergillus*-specific IgG in serum (Denning et al., 2018; Denning et al., 2016; Takazono and Izumikawa, 2018). ELISA-based commercial assays are more sensitive and specific than conventional *Aspergillus* precipitin testing (Page et al., 2017). Limitations include false-negative results in patients who fail to mount an antibody response, low sensitivity with non-fumigatus species, and false-positive results with non-CPA aspergillosis (Takazono and Izumikawa, 2018). Clinical and radiological correlation is therefore paramount (Denning et al., 2018, 2016; Takazono and Izumikawa, 2018).

The sensitivity of galactomannan in bronchoalveolar lavage (BAL) is far superior to that in serum (Sehgal et al., 2019; Shin et al., 2014). PCR-based detection of *Aspergillus* species for CPA diagnosis has been reported to be more sensitive than culture; however false-positive results may occur (Fraczek et al., 2014; Vergidis et al., 2019; Zhao et al., 2016).

Management depends on the extent and type of disease and whether the patient is a candidate for surgical resection (Denning et al., 2016). The risks and benefits of treatment must be considered in each individual patient. Data on the optimal duration and choice of antifungal agents are limited (Agarwal et al., 2013; Kohno et al., 2010). Voriconazole, isavuconazole, or itraconazole are first-line treatment options for individuals with CCA or CFA (Denning et al., 2016; Maghrabi and Denning, 2017; Patterson et al., 2016). Posaconazole is an alternative. Serum therapeutic drug monitoring is essential to optimize dosing initially (Ullman et al., 2018). Amphotericin B, micafungin, or caspofungin are intravenous alternatives if there is failure, intolerance, or resistance to the above treatment options (Denning et al., 2016; Maghrabi and Denning, 2017). With some centres in Western Europe reporting resistance rates of >25%, relative cross-resistance to multiple azoles is an increasing concern (Bueid et al., 2010; Fuhren et al., 2015).

A minimum treatment duration of 4–6 months is recommended for patients with CCA (Denning et al., 2016). However, individuals with progressive disease, poor response, or ongoing immunosuppression may require a longer duration. Lifelong therapy is required in a subset of patients with progressive disease (Patterson et al., 2016). Radiographic variation in cavity/pleural thickening and reduction/resolution of fungal ball can be used for assessment of the treatment response (Godet et al., 2016).

For individuals with a simple aspergilloma, surgical resection can prevent or treat severe haemoptysis (Patterson et al., 2016). Embolization can be done prior to surgery, or in patients for whom surgery is not possible (Denning et al., 2016).

Bronchiectasis: clinical features, management, and rehabilitation

Bronchiectasis may appear in the course of active TB or develop as a sequela of TB. A systematic review of 27 studies that evaluated patients after recovery from TB based on CT imaging reported bronchiectasis in 35–86% of patients (Meghji et al., 2016).

Bronchial stenosis and scarring in post-TB patients or external compression of bronchi by enlarged lymph nodes can lead to retention of secretions and recurrent infection, further leading to destruction and dilatation of the airways. Fibrosis and destruction of the lung parenchyma can also cause bronchiectasis by parenchymal retraction (Kim et al., 2001).

While bronchiectasis may be localized or diffuse, it most frequently affects the apical and posterior segments of the upper lobes (the most common sites of post primary TB) (Smith, 2017).

One of the major complications of bronchiectasis is frequent exacerbations of disease due to recurrent infections, progressively deteriorating lung function and reducing exercise tolerance and quality of life (QoL) (Spruit, 2014; Spruit et al., 2013). This recurring cycle of infection is due to the interplay between structural lung damage, persistent inflammation, bacterial and fungal colonization of the respiratory tract, and mucociliary insufficiency. Frequent infectious exacerbations in bronchiectasis patients are associated with higher rates of hospitalization and increased mortality, as well as incremental costs for the health system (Finch et al., 2015; Spruit, 2014; Spruit et al., 2013). Clinical manifestations of disease include a productive cough – often associated with haemoptysis. Pleuritic chest pain, dyspnoea, fever, fatigue, and weight loss are common clinical features (Smith, 2017).

Microbiology of recurrent infections exclusively in post-TB non-cystic fibrosis (CF) bronchiectatic patients is limited. However, data can be extrapolated from studies on all non-CF bronchiectasis patients, especially from settings with high TB endemicity. Commonly associated microorganisms in infectious exacerbations include *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* (Dhar et al., 2019). *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and other members of the *Pseudomonadaceae* family are increasingly recognized as causative organisms (Tunney et al., 2013; Kenna et al., 2017). This change has been attributed to advances in microbial diagnosis, enhanced sputum surveillance, and long-term suppressive antibiotic treatment (Green and Jones, 2015). NTM are also commonly isolated in bronchiectasis patients with infectious exacerbations (Chandrasekaran et al., 2018).

Medical management includes pulmonary rehabilitation (airway clearance through chest physiotherapy, inhaled hypertonic saline, and exercise if indicated) aimed at reducing the frequency and severity of recurrent infections, improving exercise tolerance and QoL (Spruit, 2014; Spruit et al., 2013).

Long-term antibiotics are given to prevent recurrent exacerbation and break this vicious cycle. Several trials have demonstrated a significant reduction in exacerbation frequency using long-term macrolide therapy (either 6 or 12 months) compared to placebo (Altenburg et al., 2013; Serisier et al., 2013). However, this practice may lead to selecting macrolide-resistant microorganisms including NTM. Inhaled antibiotics are also used to reduce the bacterial burden and typically have fewer side effects compared to oral antibiotics. However, tolerability and availability can be an issue with inhaled antibiotics. Occasionally surgical

resection of the involved segment or lobe may be indicated when there is failure of medical management of localized disease (Watanabe et al., 2006).

Non-tuberculous mycobacterial infection

Evidence suggests that the global burden of NTM infection is increasing (Brode et al., 2014). The most frequently isolated NTM from pulmonary samples is *Mycobacterium avium–intracellulare* complex (MAC) (Shah et al., 2016). *Mycobacterium kansasii* is another important cause of progressive pulmonary disease. Patients with pre-existing structural lung disease – including bronchiectasis and prior TB – are at risk of developing NTM lung disease (Fowler et al., 2006). NTM co-isolation occurs in 7–11% of patients with pulmonary TB (Damaraju et al., 2013; Hsing et al., 2013).

Clinical features of MAC lung disease are variable and non-specific and include cough, fatigue, dyspnoea, chest discomfort, haemoptysis, weight loss, and fever. *M. kansasii* presents more acutely. Radiological findings for both include parenchymal infiltration, nodules, and cavitation (Christensen et al., 1978; Swensen et al., 1994). Diagnostic criteria include compatible clinical/radiological features with either one or two positive microbiological results from bronchial lavage or sputum samples, respectively, or with suggestive histopathological features on biopsy (Griffith et al., 2007). The advent of accessible whole genome sequencing may change the diagnostic context for differentiation between infection and colonization.

The decision to start treatment for patients who meet diagnostic criteria is influenced by the severity of disease, the risk of progression, the presence of comorbidities, the tolerability of treatment, and the goals of treatment. The presence of fibrocavitary disease is associated with more rapid progression and calls for rapid start of treatment (Griffith et al., 2007). The treatment regimen depends on susceptibility to macrolides. Most guidelines suggest a three-drug regimen comprising rifampicin, ethambutol, and azithromycin or clarithromycin (Griffith et al., 2007; Haworth et al., 2017). Antibiotics can be administered three times a week for individuals with mild to moderate severity and with no evidence of fibrocavitary disease. Patients with severe disease or fibrocavitary disease require daily dosing of rifampicin, ethambutol, and azithromycin or clarithromycin, with consideration of a fourth agent in the form of either intravenous or nebulized amikacin (Haworth et al., 2017). The treatment duration is a minimum of 12 months after sputum culture conversion (Haworth et al., 2017). Therapeutic drug monitoring should be performed routinely for aminoglycosides, and should be considered for other drugs in individuals where there is a concern about malabsorption, drug–drug interactions, or suboptimal adherence (Haworth et al., 2017). There remains an urgent need for research into novel drugs or new combinations of existing drugs for NTM infections.

Prevention and vaccination

Mathematical modelling of epidemiological data suggests that there is an increase in frequency and severity of influenza-associated disease during pandemics and seasonal epidemics in individuals with pulmonary TB compared to healthy individuals (Oei and Nishiura, 2012; Noymer, 2009; Zürcher et al., 2016). Influenza and TB co-infection can impair host immune responses leading to increased susceptibility to secondary bacterial infections (Ballinger and Standiford, 2010; Small et al., 2010). The resultant increased risk of severe outcomes can potentially be mitigated by timely empirical antiviral therapy in individuals with possible influenza infection. Seasonal influenza vaccination is recommended for patients with chronic pulmonary conditions in most international guidelines (Public Health England, 2019; European Centre for Disease Prevention and Control, 2008). As the severity and chronicity of lung disease differs between individuals with treated pulmonary TB, influenza vaccination should be considered particularly for those with established chronic respiratory disease.

Cigarette smoking is a risk factor for pulmonary infections, as well as a co-factor contributing to rapid lung function deterioration, reduced exercise tolerance, and impaired QoL (Muñoz-Torrico et al., 2016; Spruit, 2014; Spruit et al., 2013). A number of studies have demonstrated a reduction in frequency and severity of exacerbations in individuals with established chronic lung disease (Willemse et al., 2004; Au et al., 2009). Additionally, population-based studies have demonstrated correlations between smoking and the development of adverse outcomes, relapse, and development of drug-resistant TB (Zhang et al., 2016). A comprehensive smoking cessation and pulmonary rehabilitation programme (Chalmers et al., 2015) is likely to be an important strategy in reducing infective exacerbations in patients with established lung disease.

Conclusions and summary

Awareness of post-TB lung health is increasingly important and gaining more attention. It is increasingly recognized that patients completing TB treatment should be followed up in time, especially if there are significant lung changes or cavities. Patients with evidence of COPD/bronchiectasis are particularly likely to experience further infectious insults and decline in lung function, with hampering of quality of life. The authors consider end of treatment spirometry, sputum for acid-fast bacilli, screening for *Aspergillus*, and a chest X-ray to be helpful when assessing a post-TB patient presenting subsequently with potential relapse of TB, non-specific infection, neoplasia, or other sequelae. Smoking cessation, vaccination, preventive antibiotics, and pulmonary rehabilitation may help curb exacerbations, reduce lung function decline, and improve quality of life.

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Approval was not required

Conflict of interest

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References

Agarwal R, Vishwanath G, Aggarwal AN, Garg M, Gupta D, Chakrabarti A. Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature. Mycoses 2013;56(5):559–70, doi:http://dx.doi.org/10.1111/myc.12075.

Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 2013;309(12):1251–9, doi:http://dx.doi.org/10.1001/jama.2013.1937.

Amaral AF, Coton S, Kato B, Tan WC, Studnicka M, Janson C, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. Eur Respir J 2015;46:1104–12.

Au DH, Bryson CL, Chien JW, Sun H, Udris EM, Evans LE, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. J Gen Intern Med 2009;24(4)457 [Epub 2 February 2009].

Ballinger MN, Standiford TJ. Postinfluenza bacterial pneumonia: host defenses gone awry. J Interferon Cytokine Res 2010;30(9):643–52, doi:http://dx.doi.org/10.1089/jir.2010.0049.

British Thoracic and Tuberculosis Association. Aspergilloma and residual tuberculous cavities—the results of a resurvey. Tubercle 1970;51(3):227–45.

Brode SK, Daley CL, Marras TK. The epidemiologic relationship between tuberculosis and non-tuberculous mycobacterial disease: a systematic review. Int J Tuberc Lung Dis 2014;18(11):1370–7, doi:http://dx.doi.org/10.5588/ijtld.14.0120.

Bueid A, Howard SJ, Moore CB, Richardson MD, Harrison E, Bowyer P, et al. Azole antifungal resistance in *Aspergillus fumigatus*: 2008 and 2009. J Antimicrob Chemother 2010;65(10):2116–8, doi:http://dx.doi.org/10.1093/jac/dkq279.

Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. Int J Infect Dis 2015;32:138–46.

Camuset J, Nunes H, Dombret MC, Bergeron A, Henno P, Philippe B, et al. Treatment of chronic pulmonary aspergillosis by voriconazole in nonimmunocompromised patients. Chest 2007;131:1435–41, doi:http://dx.doi.org/10.1378/chest.06-2441.

Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. Eur Respir J 2015;45(5):1446–62, doi:http://dx.doi.org/10.1183/09031936.00119114.

Chandrasekaran R, Mac Aogáin M, Chalmers JD, Elborn SJ, Chotirmall SH. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. BMC Pulm Med 2018;18(1):83, doi:http://dx.doi.org/10.1186/s12890-018-0638-0.

Christensen EE, Dietz GW, Ahn CH, Chapman JS, Murry RC, Hurst GA. Radiographic manifestations of pulmonary *Mycobacterium kansasii* infections. AJR Am J Roentgenol 1978;131(December (6)):985–93.

Damaraju D, Jamieson F, Chedore P, Marras TK. Isolation of non-tuberculous mycobacteria among patients with pulmonary tuberculosis in Ontario, Canada. Int J Tuberc Lung Dis 2013;17(5):676–81, doi:http://dx.doi.org/10.5588/ijtld.12.0684.

Denning DW, Page ID, Chakaya J, Jabeen K, Jude CM, Cornet M, et al. Case definition of chronic pulmonary aspergillosis in resource-constrained settings. Emerg Infect Dis 2018;24(8)e171312, doi:http://dx.doi.org/10.3201/eid2408.171312.

Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guideline for diagnosis and management. Eur Resp J 2016;47:45–68, doi:http://dx.doi.org/10.1183/13993003.00583-2015.

Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. Clin Infect Dis 2003;37 Suppl 3:S265–80.

Desai SR, Hedayati V, Patel K, Hansell DM. Chronic aspergillosis of the lungs: unravelling the terminology and radiology. Eur Radiol 2015;25(10):3100–7, doi:http://dx.doi.org/10.1007/s00330-015-3690-7.

Dhar R, Singh S, Talwar D, Mohan M, Tripathi SK, Swarnakar R, et al. Bronchiectasis in India: results from the European Multicentre Bronchiectasis Adult and Research Collaboration (EMBARC) Respiratory Research Network of India Registry. Lancet Glob Health 2019;7(9):e1269–79, doi:http://dx.doi.org/10.1016/S2214-109X(19)30327-4.

European Centre for Disease Prevention and Control. Guidance: priority risk groups for influenza vaccination. 2008. . . [Accessed on 12 February 2020] https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/0808_GUI_Priority_Risk_Groups_for_Influenza_Vaccination.pdf.

Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc 2015;12(11):1602–11, doi:http://dx.doi.org/10.1513/AnnalsATS.201506-333OC.

Fowler SJ, French J, Screaton NJ, Foweraker J, Condliffe A, Haworth CS, et al. Non-tuberculous mycobacteria in bronchiectasis: prevalence and patient characteristics. Eur Respir J 2006;28(6):1204–10.

Fraczek MG, Kirwan MB, Moore CB, Morris J, Denning DW, Richardson MD. Volume dependency for culture of fungi from respiratory secretions and increased sensitivity of *Aspergillus* quantitative PCR. Mycoses 2014;57:69–78, doi:http://dx.doi.org/10.1111/myc.12103.

Fuhren J, Voskuil WS, Boel CH, Haas PJ, Hagen F, Meis JF, et al. High prevalence of azole resistance in *Aspergillus fumigatus* isolates from high-risk patients. J Antimicrob Chemother 2015;70(10):2894–8, doi:http://dx.doi.org/10.1093/jac/dkv177.

Glaser S, Kruger S, Merkel M, Bramlage P, Herth FJF. Chronic obstructive pulmonary disease and diabetes mellitus: a systematic review of the literature. Respiration 2015;89:253–64.

Godet C, Laurent F, Bergeron A, Ingrand P, Beigelman-Aubry C, Camara B, et al. CT imaging assessment of response to treatment in chronic pulmonary aspergillosis. Chest 2016;150(July (1)):139–47, doi:http://dx.doi.org/10.1016/j.chest.2016.02.640.

Green H, Jones AM. The microbiome and emerging pathogens in cystic fibrosis and non-cystic fibrosis bronchiectasis. Semin Respir Crit Care Med 2015;36(2):225–35, doi:http://dx.doi.org/10.1055/s-0035-1546752.

Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment and prevention of non-tuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175(4):367–416.

Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72(Suppl. 2), doi:http://dx.doi.org/10.1136/thoraxjnl-2017-210927 ii1–ii64.

Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax 2000;55:32–8.

Hsing SC, Weng SF, Cheng KC, Shieh JM, Chen CH, Chiang SR, et al. Increased risk of pulmonary tuberculosis in patients with previous non-tuberculous mycobacterial disease. Int J Tuberc Lung Dis 2013;17(7):928–33, doi:http://dx.doi.org/10.5588/ijtld.12.0675.

Jewkes J, Kay PH, Paneth M, Citron KM. Pulmonary aspergilloma: analysis of cavitating invasive pulmonary aspergillosis in immunocompromised patients. Ann Thorac Surg 1983;53:621.

Jhun BW, Jung WJ, Hwang NY, Park HY, Jeon K, Kang ES, et al. Risk factors for the development of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease. PLoS One 2017;12(11)e0188716, doi:http://dx.doi.org/10.1371/journal.pone.0188716.

Kenna DTD, Lilley D, Coward A, Martin K, Perry C, Pike R, et al. Prevalence of *Burkholderia* species, including members of Burkholderia cepacia complex, among UK cystic and non-cystic fibrosis patients. J Med Microbiol 2017;66(4):490, doi:http://dx.doi.org/10.1099/jmm.0.000458.

Kim HY, Song KS, Goo JM, Lee JS, Lee KS, Lim TH. Thoracic sequelae and complications of tuberculosis. Radiographics 2001;21(4):839–58.

Kohno S, Izumikawa K, Ogawa K, Kurashima A, Okimoto N, Amitani R, et al. Intravenous micafungin versus voriconazole for chronic pulmonary aspergillosis: a multicenter trial in Japan. J Infect 2010;61(5):410–8, doi:http://dx.doi.org/10.1016/j.jinf.2010.08.005.

Lowes D, Al-Shair K, Newton PJ, Morris J, Harris C, Rautemaa-Richardson R, et al. Predictors of mortality in chronic pulmonary aspergillosis. Eur Respir J 2017;49(2), doi:http://dx.doi.org/10.1183/13993003.01062-2016 pii: 1601062.

Maghrabi F, Denning DW. The management of chronic pulmonary aspergillosis: the UK national aspergillosis centre approach. Curr Fungal Infect Rep 2017;11(4):242–51, doi:http://dx.doi.org/10.1007/s12281-017-0304-7.

Meghji J, Simpson H, Squire SB, Mortimer K. A systematic review of the prevalence and pattern of imaging defined post-TB lung disease. PLoS One 2016;11:e0161176, doi:http://dx.doi.org/10.1371/journal.pone.0161176.

Muñoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, et al. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis?. J Bras Pneumol 2016;42:374–85.

Naito M, Kurahara Y, Yoshida S, Ikegami N, Kobayashi T, Minomo S, et al. Prognosis of chronic pulmonary aspergillosis in patients with pulmonary non-tuberculous mycobacterial disease. Respir Investig 2018;56(4):326–31, doi:http://dx.doi.org/10.1016/j.resinv.2018.04.002.

Noymer A. Testing the influenza–tuberculosis selective mortality hypothesis with Union Army data. Soc Sci Med 2009;68(9):1599–608.

Oei W, Nishiura H. The relationship between tuberculosis and influenza death during the influenza (H1N1) pandemic from 1918–19. Comput Math Methods Med 2012;2012:124861, doi:http://dx.doi.org/10.1155/2012/124861.

Ohba H, Miwa S, Shirai M, Kanai M, Eifuku T, Suda T, et al. Clinical characteristics and prognosis of chronic pulmonary aspergillosis. Respir Med 2012;106(5):724–9, doi:http://dx.doi.org/10.1016/j.rmed.2012.01.014.

Page ID, Richardson MD, Denning DW. Comparison of six Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis (CPA). J Infect 2017;72:240–9, doi:http://dx.doi.org/10.1016/j.jinf.2015.11.003.

Pasqualotto AC, Denning DW. An aspergilloma caused by *Aspergillus flavus*. Med Mycol 2008;46(3):275–8.

Patterson TF, Thompson GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63(August (4)):e1–e60, doi:http://dx.doi.org/10.1093/cid/ciw326.

Public Health England. Influenza: the Green book. 2019. . . [Accessed on 12 February 2020]. [chapter 19] https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19.

Schweer KE, Bangard C, Hekmat K, Cornely OA. Chronic pulmonary aspergillosis. Mycoses 2014;57(5):257–70, doi:http://dx.doi.org/10.1111/myc.12152.

Sehgal IS, Dhooria S, Choudhary H, Aggarwal AN, Garg M, Chakrabarti A, et al. Utility of serum and bronchoalveolar lavage fluid galactomannan in diagnosis of

chronic pulmonary aspergillosis. J Clin Microbiol 2019;57(3), doi:http://dx.doi.org/10.1128/JCM.01821-18 e01821-18.
Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 2013;309(12):1260–7, doi:http://dx.doi.org/10.1001/jama.2013.2290.
Severo LC, Geyer GR, Porto Nda S, Wagner MB, Londero AT. Pulmonary *Aspergillus* niger intracavitary colonization. Report of 23 cases and a review of the literature. Rev Iberoam Micol 1997;14(3):104–10.
Shah NM, Davidson JA, Anderson LF, Lalor MK, Kim J, Thomas HL, et al. Pulmonary Mycobacterium avium-intracellulare is the main driver of the rise in non-tuberculous mycobacteria incidence in England, Wales and Northern Ireland, 2007–2012. BMC Infect Dis 2016;16:195, doi:http://dx.doi.org/10.1186/s12879-016-1521-3.
Shin B, Koh WJ, Jeong BH, Yoo H, Park HY, Suh GY, et al. Serum galactomannan antigen test for the diagnosis of chronic pulmonary aspergillosis. J Infect 2014;68:494–9, doi:http://dx.doi.org/10.1016/j.jinf.2014.01.005.
Small CL, Shaler CR, McCormick S, Jeyanathan M, Damjanovic D, Brown EG, et al. Influenza infection leads to increased susceptibility to subsequent bacterial superinfection by impairing NK cell responses in the lung. J Immunol 2010;184(4):2048–56, doi:http://dx.doi.org/10.4049/jimmunol.0902772.
Smith MP. Diagnosis and management of bronchiectasis. CMAJ 2017;189(24):E828–35, doi:http://dx.doi.org/10.1503/cmaj.160830.
Spruit MA. Guidelines ERS pulmonary rehab — pulmonary rehabilitation. Eur Respir Rev 2014;23(131):55–63, doi:http://dx.doi.org/10.1183/09059180.00008013.
Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188(8):e13–64, doi:http://dx.doi.org/10.1164/rccm.201309-1634ST.
Swensen SJ, Hartman TE, Williams DE. Computed tomographic diagnosis of Mycobacterium avium-intracellulare complex in patients with bronchiectasis. Chest 1994;105(1):49–52.
Takazono T, Izumikawa K. Recent advances in diagnosing chronic pulmonary *Aspergillosis*. Front Microbiol 2018;9:1810, doi:http://dx.doi.org/10.3389/fmicb.2018.01810.
Tunney MM, Einarsson GG, Wei L, Drain M, Klem ER, Cardwell C, et al. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. Am J Respir Crit Care Med. 2013;187(May (10)):1118–26, doi:http://dx.doi.org/10.1164/rccm.201210-1937OC.
Ullman AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect 2018;24 Suppl 1 (May):e1–e38, doi:http://dx.doi.org/10.1016/j.cmi.2018.01.002.
van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J 2010;35:27–33.
Vergidis P, Moore CB, Novak-Frazer L, Rautemaa-Richardson R, Walker A, Denning DW, et al. High-volume culture and quantitative real-rime PCR for the detection of *Aspergillus* in sputum. Clin Microbiol Infect 2019;, doi:http://dx.doi.org/10.1016/j.cmi.2019.11.019 pii: S1198-743X(19)30619-6.
Watanabe M, Hasegawa N, Ishizaka A, Asakura K, Izumi Y, Eguchi K, et al. Early pulmonary resection for Mycobacterium avium complex lung disease treated with macrolides and quinolones. Ann Thorac Surg 2006;81(6):2026.
Willemse BW, Postma DS, Timens W, ten Hacken NH. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. Eur Respir J 2004;23(3):464.
Zhang C, Wang Y, Shi G, Han W, Zhao H, Zhang H. Determinants of multidrug-resistant tuberculosis in Henan province in China a case control study. BMC Public Health 2016;16:42, doi:http://dx.doi.org/10.1186/s12889-016-2711-z.
Zhao Y, Garnaud C, Brenier-Pinchart MP, Thiébaut-Bertrand A, Saint-Raymond C, Camara B, et al. Direct molecular diagnosis of *Aspergillosis* and CYP51A profiling from respiratory samples of French patients. Front Microbiol 2016;7:1164, doi:http://dx.doi.org/10.3389/fmicb.2016.01164.
Zürcher K, Zwahlen M, Ballif M, Rieder HL, Egger M, Fenner L. Influenza pandemics and tuberculosis mortality in 1889 and 1918: analysis of historical data from Switzerland. PLoS One 2016;11(10)e0162575, doi:http://dx.doi.org/10.1371/journal.pone.0162575.