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Nontuberculous Mycobacterial Pulmonary Disease

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1. Introduction

Tuberculosis (TB) is an infectious and transmissible disease caused by *Mycobacterium tuberculosis* and closely related mycobacterial species (*M. bovis*, *M. africanum*, and *M. microti*). These species, obligate pathogens, compose what is known as the *M. tuberculosis complex*. Nontuberculous mycobacterial (NTM) species are mycobacterial species other than those belonging to the *Mycobacterium tuberculosis complex*. Nontuberculous mycobacteria are generally free-living organisms that are ubiquitous in the environment. There have been more than 140 NTM species identified. In 1959, Runyon proposed a classification of NTM into four major groups, based on growth rate and colony pigmentation (Runyon EH , 1959).

There is an increasing number of clinical isolates of NTM in many countries and growing awareness of their ability to cause disease (American Thoracic Society [ATS], 2007). Nontuberculous mycobacteria are capable of causing a wide range of infections in humans with pulmonary NTM disease being the most common, especially in patients with pre-existent pulmonary disease (ATS, 2007). They are mainly opportunistic pathogens that can occasionally cause severe disseminated diseases, especially in patients with systemic impairment of immunity. Identification of specific species of NTM is important because of the variation in antimicrobial susceptibility and treatment options.

Nontuberculous mycobacteria can be divided into slowly growing and rapidly growing mycobacteria (RGM). The former constitute members of the Runyon group I to group III, whereas the latter are equivalent to the members of Runyon group IV. (Table 1) (Runyon E, 1965) Pulmonary disease is primarily caused by *M. avium complex (MAC)* and *M. kansasii (*ATS, 2007*)*. Other species include *M. abscessus*, *M. fortuitum*, *M. xenopi*, *M. malmoense*, *M. szulgai*, and *M. simiae*. In contrast to *M. tuberculosis*, isolation of NTM does not necessarily mean that patient has the disease though it can be isolated transiently from respiratory specimens. In order to assist clinicians with the difficult task of trying to determine if a given NTM species is causing disease to a patient, a set of criteria utilizing clinical, radiographic, and microbiologic parameters has been developed. Furthermore, the degree of evidence to support the choice of treatment is limited because a few clinical trials have been conducted, especially for disease due to less prevalent NTM species.

Mycobacterium tuberculosis complex
M. tuberculosis
M. bovis
M. africanum
M. microti
Slowly growing mycobacteria
Runyon Group I, Photochromogenes
M. kansasii
M. marinum
Runyon Group II, Scotochromogenes
M. gordonae
M. scrofulaceum
Runyon Group III, Non-chromogenes
M. avium complex – M. avium, M. intracellulare
M. terrae complex
M. ulcerans
M. xenopi
M. simiae
M. malmoense
M. szulgai
M. asiaticum
Rapidly growing mycobacteria
Runyon group IV
M. fortuitum
M. chelonae
M. abscesus

Table 1. Classification of mycobacterial species commonly causing human disease

Current guidelines are mainly based on case reports and clinical experience (ATS 2007, British thoracic society [BTS], 1999)

2. Epidemiology and prevalence

Tuberculosis still remains an important public health problem worldwide, with more than 9 million new cases of tuberculosis reported every year and decrease of incidence of less than 1% per year. On the other hand, in the industrialized world, the incidence of *M. tuberculosis*

infections has been decreasing, while the incidence of NTM pulmonary infections is increasing.

Although both *M. tuberculosis* and NTM cause chronic lung infections, only *M. tuberculosis* spreads from person to person by inhalation of organisms expectorated into the air. Nontuberculous mycobacteria infections are not considered contagious. Since reporting NTM pulmonary disease to public health departments is not obligatory, the exact number of the infected remains unknown. An increase in the frequency of NTM infections and NTM pulmonary disease has been indicated in a number of worldwide surveys and population-based studies during the last few decades (AST, 2007; Maras et al, 2007; Iseman & Marras, 2008; Henry et al, 2004; Thomson & Yew, 2009).

Postulated reasons for this increase include a rise in prevalence of HIV infections and other acquired immunocompromised states, increased awareness of these organisms as potential pathogens, a better understanding of clinical-pathological relationship between host and pathogen, advances in methods of detection of the organisms, an aging population (as this is often a disease of the elderly), increased survival of patients with predisposing conditions such as cystic fibrosis and COPD, and increased environmental exposure (ATS, 2007; Thomson & Yew, 2009).

Nontuberculous mycobacteria disease is not a reportable condition in most countries because it is not considered a public health concern on account of unknown or non-existing evidence of human-to-human transmission (ATS, 2007). However, the organisms are ubiquitous in the environment, oligotrophic and many NTM pathogens have been isolated from potable water where they can be found forming biofilms (Falkingham et al, 2001). *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii* and RGM such as *M. abscessus* and *M. fortuitum* constitute the main species associated with human pulmonary disease. (ATS, 2007; Thomsen et al, 2002; Martin-Casabona et al, 2004). It has been shown in multiple already published studies that geography has a prominent role in the epidemiology of NTM pulmonary disease. Thus, *M. xenopi* is relatively more common in the south-east and in the west of Europe (Marusic et al, 2009; van Ingen et al, 2008; Hanry et al, 2004; Dailloux et al, 2006) and in Canada (Varadi & Marras, 2009), while *M. malmoense* is relatively more common in the north of Europe (Abgueguen et al, 2010; Petrini, 2006; Thomsen et al, 2002; Henry et al, 2004).

3. Pulmonary disease characteristics and population at risk

The symptoms of NTM pulmonary disease are variable and nonspecific. Common symptoms are chronic or recurring cough, while others such as sputum production, fatigue, malaise, dyspnea, fever, hemoptysis and weight loss become more prevalent with advanced NTM lung disease.

Pulmonary NTM disease has three distinct presentations: cavitary disease (resembling conventional tuberculosis) (Figure 1) (Moore, 1993; Patz et al, 1995; Jeong et al, 2004), nodular-bronchiectatic disease (Figure 2) commonly affecting the right middle lobe and lingula (Moore, 1993; Patz et al, 1995; Jeong et al 2004; Reich & Johnson, 1992) and the rarest form - hypersensitivity pneumonitis. There are mixed disease forms with infiltrates, nodes, bronchiectasis and interstitial changes (Figure 3).

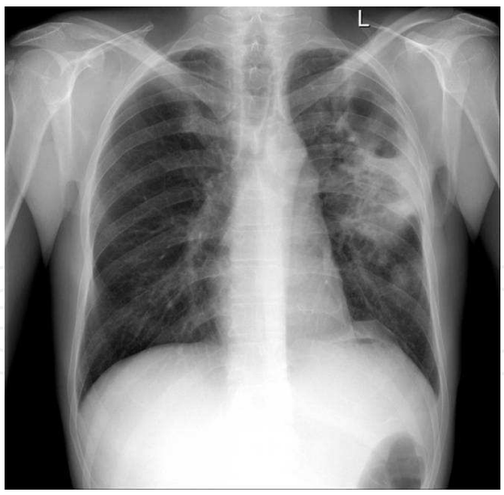

Fig. 1. Extensive infiltrate with cavitation in the left lung

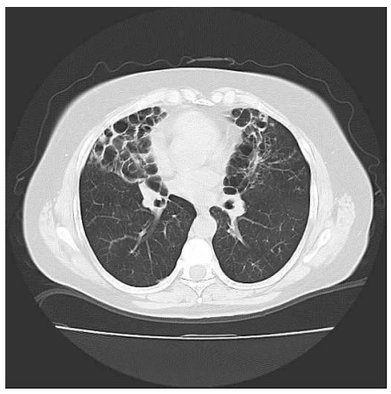

Fig. 2. Nodular-bronchiectatic disease in the middle lobe and lingula

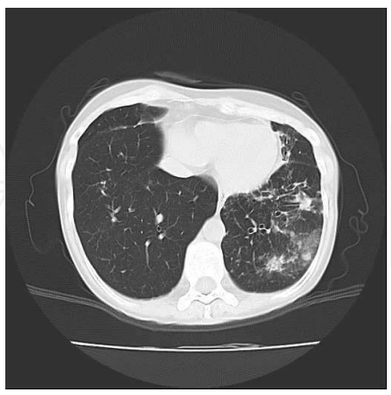

Fig. 3. Mixed disease form; infiltrate, nodes, bronchiectasis, "ground glass" interstitial pattern and tiny centrilobular nodes in left lower lobe

HIV-positive and other immunodeficient patients, on the other hand, often have hilar and mediastinal lymphadenopathy with systemic spread but without pulmonary infiltrate (dos Santos et al, 2008). Patients with NTM pulmonary disease often have predisposing

structural lung disease, i.e. chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, pneumoconiosis, prior tuberculosis, alveolar proteinosis, or chronic aspiration (ATS, 2007; Field & Cowie, 2006).

Among women with pulmonary disease, there is often constellation of physical findings such as bronchiectasis, thin body habitus and mitral valve prolapse (Prince et al, 1989; Kim et al, 2008). The reason for this association has not been determined and no significant immunological abnormality has been identified.

4. Diagnosis of NTM pulmonary infections

Patients seeking treatment who have respiratory samples positive for acid-fast bacilli (AFB) present a public health dilemma. Although Mycobacterium tuberculosis and NTM cause chronic lung infections, only tuberculosis (TB) spreads from person to person by inhalation of organisms expectorated into the air, while NTM infections are acquired directly from the environment. Diagnosing mycobacterial infections is often quite a challenge. Under the microscope, NTM and *M. tuberculosis* appear similar. Careful laboratory investigations must be performed to differentiate them. The definitive identification of mycobacterial species, which can take several weeks, and the inability to quickly distinguish NTM from TB on clinical grounds makes it difficult for public health officials to make decisions regarding contact investigations and isolation. Mycobacterial pulmonary disease usually progresses slowly, and clinical diagnosis starts with the exclusion of other possible causes. Differential diagnosis includes tuberculosis and fungal infection, especially the classical form of NTM infection which mimics *M. tuberculosis* infection. The development and use of molecular techniques to differentiate between the mycobacteria strains made it possible to solve some of these problems. The first step in diagnosing an NTM infection is suspecting an underlying cause of the symptoms or radiographic findings. Chronic cough (lasting >3 weeks), fatigue, night sweats, and weight loss should make clinicians consider mycobacterial infections. Even though dyspnoea is usually more related to underlying lung disease, occasionally patients with the nodular/bronchiectatic disease can have bronchiolitis and air trapping associated with dyspnoea. Haemoptysis occurs in more advanced lung disease, especially with cavitations and advanced bronchiectasis. A chest radiograph, or more likely, high resolution computed tomography (HRCT), could show some radiomorphologic changes to be the first sign of presence of an NTM infection. Respiratory specimens should be obtained and sent for mycobacterial culture.

4.1 Imaging of NTM pulmonary infections

A chest radiograph is the first method to be used when suspecting an NTM pulmonary disease but it may be adequate for evaluating only patients with fibrocavitary disease. It is widely available and convenient and exposes patient to a very low irradiation dose. On the other hand, chest radiograph is far less sensitive and specific than HRCT, especially in detection of bronchiectasis, small nodules and other interstitial lung changes. Since nodular/bronchiectatic form of pulmonary NTM infection is not rare, HRCT should be used in patients with high clinical suspicion even if chest x-ray finding is normal. In case of clinical suspicion of hypersensitivity pneumonitis, HRCT is definitively the only method of choice. Even though some differences have been reported, it is impossible to differentiate

NTM pulmonary disease from TB pulmonary disease relying on radiographic appearance alone. Compared with radiographic findings in TB, patients with NTM disease and predominantly fibrocavitary radiographic changes tend to have following characteristics: thin-walled cavities with less surrounding parenchymal opacity, more contiguous spread of disease, and production of more marked involvement of pleura over the involved area of the lungs (ATS, 2007). Basal pleural disease is not often found and pleural effusion is rare (ATS, 2007). At patients with predominantly nodular/bronchiectatic disease, the abnormalities on chest radiograph and HRCT are primarily found in the mid and lower lung field. Radiographic follow-up during the treatment should be performed using either chest radiograph in patients with predominantly cavitary disease, or HRCT in those with interstitial form of the disease. Confirmation of complete resolution and an insight into possible residual scarring can be done only by using HRCT.

4.2 Laboratory features of NTM

Using modern microbiology laboratory methods, including liquid culture media, NTM growth can be detected by culture from a patient's specimens 1-3 weeks after the incubation. (Leitritz et al, 2001) Most rapid growing NTM will grow in 7-10 days. Slow growers can grow in 1-3 weeks, but may take much longer. Therefore, cultures are usually kept for 6-8 weeks before being regarded as negative. At patients colonized with *Pseudomonas aeruginosa* or other bacterial pathogens, sputum specimens can be overgrown before NTM growth appears. Special decontamination methods are often necessary to reduce this overgrowth, but decontamination also reduces the yield of mycobacteria and persistence is required if there is a high clinical suspicion of NTM disease with these patients. With the recovery of an organism by culture, DNA probes are commercially available to identify some of the NTM (Tortoli et al, 2010).

Other organisms have traditionally been identified by combination of biochemical testing, high-performance liquid chromatography (HPLC) and genetic sequencing of conserved regions. Partial sequencing of a segment of 16S ribosomal RNA has been used to identify those species not identified by other means. (Cloud et al, 2002, 2005) Current guidelines of American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) (ATS, 2007) state that routine testing of MAC species for antimicrobial susceptibility (other than clarithromycin) is generally not recommended because of the paucity evidence correlating *in vitro* and *in vivo* results (ATS, 2007). They do recommend clarithromycin susceptibility testing for new, previously untreated MAC isolates as macrolide resistance has been associated with a poorer outcome. It should also be performed for MAC isolates from patients who have relapsed from apparently successful treatment or those who have failed macrolide treatment (ATS, 2007). Previously untreated *M. kansasii* strains should be tested *in vitro* to rimfapicin only (ATS 2007) and against a panel of secondary agents if shown to be resistant to rimfapicin. RGM should be tested against a panel of eight antimicrobials, including clarithromycin, amikacin, cefoxitin, ciprofloxacin, doxycicline, linezolid, sulphamethoxazole and tobramycin.

4.3 Diagnostic criteria

Even after an NTM has been isolated and identified, the patient may still not have the disease because NTM can be isolated transiently from respiratory specimens. In order to

help clinicians with the difficult task of trying to determine if a given NTM species is causing disease in a patient the ATS/IDSA developed a set of criteria that utilized clinical, radiographic, and microbiologic parameters (ATS, 2007) (Table 2).

Clinical criteria Compatible respiratory symptoms Appropriate exclusion of other diagnoses, especially tuberculosis and mycosis
AND
Radiographic criteria Nodular or cavity opacities on chest radiograph, or a HRCT scan that shows multifocal bronchiectasis with or without multiple small nodules
AND
Microbiological criteria
Positive culture results from at least two or three separately expectorated sputum samples with positive or negative AFB smear, respectively
OR
Positive culture results from at least one bronchial wash or lavage
OR
Transbronchial or other lung biopsy with mycobacterial histopatological features and one positive sputum culture for NTM

Table 2. Summary of the ATS/IDSA criteria for diagnosis of pulmonary NTM diseases

The significance of an isolate also varies with the species of mycobacteria. Isolation of mycobacteria like *M. gordonae*, *M. flavescens*, *M. terrae complex* or *M. triviale* usually indicates transient colonization or possible contamination of the sample. However, *M. szulgai* is rarely isolated from the environment and a single positive culture provides pathological significance (ATS, 2007).

5. Treatment and prognosis of NTM pulmonary infections

The currently used regimen for TB treatment consists of four drugs: rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB), for the duration of six to nine months. Treatment of pulmonary NTM infections is usually more complicated than treatment of tuberculosis. Drugs, administration frequency, and duration of therapy will vary depending on species of NTM causing the disease, extent and the site of infection. Some antituberculosis drugs are also active against some NTM species. However, treatment of most NTM species also requires administration of antibiotics that are not typically used to treat tuberculosis. The prognosis for NTM pulmonary disease depends on specific species and subspecies involved and their drugs susceptibility pattern, presence of other medical problems and whether or not patient can tolerate the treatment regimen. Cure rate for the disease caused by *M. kansasii* is similar to *M. tuberculosis* round 90%, while that for the disease caused by *M. avium* is 30-85%. Complete recovery is seldom achieved in patients with pulmonary *M. abscessus* infection (ATS, 2007).

Diagnosing pulmonary NTM infection/disease does not equate the need for immediate treatment since treatment usually involves combination antibiotic therapy for 12-24 months and constitutes an important undertaking for the patient. Lung involvement may range in severity from mild clinical (indolent) infection to disease associated with extensive invasion or destruction of the lungs. In some cases the disease remits spontaneously. Most of the early studies on NTM covered MAC, *M. kansasii* and *M. abscessus* and developed diagnostic criteria and treatment regimens best suitable for these species. There is not enough knowledge about most other NTM to be certain that the diagnostic criteria are universally applicable for all NTM respiratory pathogens (ATS, 2007). Generally, patients respond best to NTM treatment first time it is administered. Therefore, it is important that patients initially receive a recommended multi-drug regimen (ATS, 2007).

The British Thoracic Society (BTS) and ATS/IDSA have published guidelines for the management of the disease caused by NTM. Guidelines published by ATS/IDSA have been updated in 2007 providing an extensive review of the available literature on NTM disease combined with expert opinion. The recommended criteria are thus based on several smaller prospective non-randomized controlled studies at the US patients.

It is very difficult to compare many different studies in pulmonary NTM disease considering the geographic differences in patient populations, mixture of disease types, severity of disease, differing species of NTM, drugs and therapy protocols used and different study design and analysis. The BTS guidelines are predominantly based on two large randomized controlled trials performed in patients of the UK and Europe (BTS, 2001). All of the mentioned differences are factors contributing to the significant heterogeneity of findings and hence the recommendations made by the Societies.

Treatment of pulmonary disease should be considered in patients who meet clinical, radiological, and microbiologic criteria for NTM disease. Two main factors to consider regarding initiation of therapy should be pathogenicity of species and rate of disease progression. Therapy for NTM requires prolonged administration of multiple drugs and is associated with significant side effects. The decision to institute treatment in patients with non-cavitary disease who do not have clearly progressive pulmonary disease should be made carefully, after a period of clinical and radiological follow-up. The aim of therapy is a 12-month period of negative sputum cultures.

5.1 Specific antimicrobial treatment guidelines

5.1.1 MAC lung disease

Recommended treatment regimens for MAC lung disease are summarized in Table 3. There are still a number of controversies and unresolved questions regarding the management of MAC lung disease.

First, there is no demonstrated superiority of one macrolide among the two agents regarding efficacy or risk of resistance. It seems that macrolides have helped improving treatment of MAC lung disease (Kobashi YMT, 2004) though not all studies have supported this (Jenkins et al, 2008).

Second, there has also been no demonstrated superiority of one rifamycin (rifabutin or rifampicin) in the treatment of MAC lung disease, but because of frequent adverse events,

Nodular/bronchiectatic disease	
All given 3 times weekly	Clarithromycin (1000 mg) or azithromycin (500 mg) +
	Rifampin (600 mg) +
	Ethambutol (25 mg/kg)
Fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease	
All given daily	Clarithromycin (500–1000 mg) or azithromycin (250 mg) +
	Rifampin (600 mg) or rifabutin (150–300 mg) +
	Ethambutol (15 mg/kg)
	Consider adding 3-times-weekly amikacin or streptomycin early in therapy (e.g., for the first 8 weeks)
Duration:	Treat until cultures have been negative on therapy for 1 year.

Table 3. Recommended treatment regimens for MAC pulmonary disease

most experts recommend the use of rifampicin (Griffith et al, 1995) Regarding the use of an amynoglicoside in the initial phase of treatment, the majority of early macrolides studies performed in the USA included 2- to 3-month period of intermittent amynoglicoside. Furthermore, Kobashi has shown that sputum conversion rates, relapse rates and overall outcomes were better in the cohort that received amynoglicoside (Kobashi YMT, 2004).

For hypersensitivity pneumonitis due to MAC, removal from environmental exposure is mandatory. Corticosteroids and/or anti-microbial drugs might be required in some cases and usually a shorter regimen of 3-6 months may be appropriate. (Hanak et al, 2006)

5.1.2 *M. kansasii* lung disease

Recommended treatment regimen for *M. kansasii* lung disease is summarized in Table 4. For susceptible strains, rifampin is the foundation of a multiple-drug regimen. Resistance to rifampin may develop, in which case a 3-drug regimen should be chosen on the basis of in vitro susceptibility testing (e.g., clarithromycin or azithromycin, moxifloxacin, ethambutol, sulphamethoxazole, or streptomycin) (ATS 2007).

5.1.3 *M. xenopi*, *M. malmoense* and *M. szulgai* lung disease

M. xenopi has variable drug susceptibility testing results, especially regarding the first-line antituberculotic agents (ATS, 2007). The clinical response to treatment does not always correlate well with drug susceptibility testing results. The ATS proposed regimen is a combination of ethambutol, rifampicin, isoniasid and clarithromycin with or without an initial course of streptomycin. *M. malmoense* can be difficult to treat. A combination of rifampicin and ethambutol with or without isoniasid has shown some effectiveness (BTS 2001). *M. szulgai* is susceptible in vitro to most antituberculosis drugs, as well as to floroquinolones and macrolides (Sanchez-Alarcos et al, 2003) and a 3- or 4-drug regimen that includes 12 months of negative sputum cultures while on therapy is recommended (ATS, 2007)

Rifampin	600 mg/d, +
Isoniazid	300 mg/d, +
Ethambutol	15 mg/kg/d
Duration:	at least 12 months after the last positive sputum culture

Table 4. Recommended treatment regimens for rifampicin-susceptible *Mycobacterium kansasii* pulmonary disease

5.1.4 Lung disease caused by rapidly growing mycobacteria

Three main species of RGM causing pulmonary disease are *M. abscessus*, *M. chelonae* and *M. fortuitum*. The choice of treatment relies on guidance from susceptibility testing as there are no results from large-scale clinical studies available. *M. abscessus* pulmonary disease can be especially difficult to treat.

The treatment usually involves combination of amikacin, cefoxitin/imipenem and clarithromycin. The summary of proposed treatment for RGM lung disease is shown in Table 5. For many patients, realistic objectives of treatment are to help controlling symptoms and disease progression rather than curing the infection. Surgery can be considered for localized disease.

5.1.5 Surgical treatment

Surgical resection of limited (focal) pulmonary NTM disease in a patient with an adequate cardiopulmonary reserve can be successful in combination with multi-drug treatment regimens for MAC and *M. abscessus* disease (ATS, 2007). In addition, in an extensive disease, the excision of large cavitary mycobacterial foci might assist medical management of remaining lesions. However, according to ATS guidelines, surgery should only be performed in medical centres with considerable medical and surgical expertise in management of patients with NTM disease.

	Active drugs	*Surgery*
M. abscessus	Clarithromycin	++
	Amikacin	
	Cefoxitin	
	Imipenem	
M. chelonae	Tobramycin	+
	Clarithromycin	
	Linezolid	
	Imipenem	
	Amikacin	
	Doxycycline	
	Ciprofloxacin	
M. fortuitum	Amikacin	+
	Ofloxacin/Ciprofloxacin	
	Imipenem	
	Sulphonamides	
	Clarithromycin	
	Doxycycline	

Table 5. Treatment of lung disease due to rapidly growing mycobacteria

6. Where do we go from here?

Given the recent worldwide increase in NTM infections and in comparison to other lung diseases, relatively little progress has been made in understanding, preventing or treating pulmonary NTM disease. It is still not clear why some people develop infections while most do not. Even though information is provided from basic research and a few clinical trials, better understanding of the pathogenesis of these infections is needed in order to improve prevention of harm from these ubiquitous environmental bacteria. As NTM lung diseases are generally difficult to treat, new drugs are needed to advance therapy. Furthermore, randomized controlled trials in well-described patients would provide stronger evidence-based data to guide therapy of NTM lung diseases. Elucidation of the mechanism behind host susceptibility will also add invaluable information so that therapy could be directed towards the underlying cause for the establishment of infection. Finally, environmental factors contributing to the increased prevalence of infection should also be explored in order to reduce infection and re-infection of susceptible patients.

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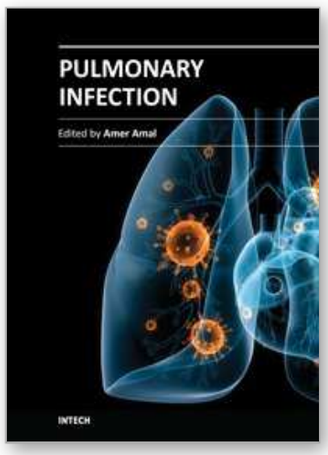

Pulmonary Infection
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Pulmonary infections are notorious in causing considerable morbidity and mortality. Caused by bacteria, viruses or fungi, respiratory infections require distinct knowledge of recent advances in pathogenesis. Progress in the understanding of immunopathogenesis of Acinetobacter baumannii infection will explain how an atypical organism establishes infection. The chapter regarding pulmonary nontuberculous mycobacterial infections in the State of Para depicts a unique study in an endemic region for tuberculosis in North of Brazil. The diagnosis and treatment of latent tuberculosis is a formidable challenge. Thus, new developments in diagnosis and treatment of latent tuberculosis are included in this book. Challenging in their diagnosis, nontuberculous mycobacterial pulmonary diseases require special education for management. The problems of respiratory infections in the immunocompromised host are increasing in numbers and in resilience to treatment. Therefore, the chapter describing the host immune responses against pulmonary fungal pathogens comes as a necessary section in this book. The insight brought forth from this book can be valuable for both clinicians and scientists.

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