Pulmonary Pharmacology & Therapeutics 23 (2010) 389–396

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

The therapeutic approach to non-tuberculous mycobacterial infection of the lung

Emmet E. McGrath*, Paul B. Anderson

Department of Respiratory Medicine, Northern General Hospital, Sheffield S5 7AU, UK

ARTICLE INFO

Article history:
Received 21 February 2010
Received in revised form
28 May 2010
Accepted 3 June 2010

Keywords:
Non-tuberculous mycobacteria
ATS/IDSA guidelines
Drug regimen
Drug toxicity
In vivo susceptibility testing
Novel therapies

ABSTRACT

Non-tuberculous mycobacteria (NTM) are a group of alcohol fast, aerobic, nonmotile bacteria that are found in the environment. Recent reports indicate that their incidence and prevalence is increasing and guidelines have been developed laying down criteria for diagnosis. The treatment of these mycobacteria may be difficult, in many cases involving complex regimens containing multiple drugs. While traditional anti-tuberculosis medications are frequently used, specific therapeutic regimens depend on the organism isolated, *in vitro* susceptibility testing, drug tolerance and toxicity and concomitant medical disorders. In this review, we describe the diagnosis and treatment of the more important lung pathogens, describing complexities and controversies surrounding treatment with traditional, adjunctive and the newer and more experimental agents.

1. Introduction

Non-tuberculous mycobacteria are a group of organisms found in soil, treated and untreated water, animals and food [1,2]. Traditionally NTM have been divided into slow growing (e.g. MAC, *kansasaii*, *malmoense*, *xenopi*) and rapid growing mycobacteria (e.g. *fortuitum*, *abscessus*, *chelonae*) depending on their behaviour in culture. Unlike *Mycobacterium tuberculosis* and *Mycobacterium leprae*, they generally do not cause disease in humans but when they do, give rise to lung infection, lymphadenitis and in susceptible individuals, disseminated disease [3].

Presentation is often very similar to that of TB, with cough, fever, sweats, fatigue, weight loss, haemoptysis and upper lobe cavitation well described [3].

Apart from cavitatory lung disease, nodular bronchiectasis and hypersensitivity pneumonitis have also been described [3].

In recent years the incidence and prevalence of NTM has been increasing, despite the fact that human to human transmission has never been demonstrated [4]. A proportion of this increase is attributed to improved microbiological and laboratory techniques and analysis as well as the increased physician awareness that has lead to more samples being sent to the laboratory. More species have also been identified through the development of gene sequence analysis. To date, over 125 species have been described although only a small proportion of these are recognised as important lung pathogens [5].

Given the increase in incidence and prevalence of these mycobacteria, their presence in culture must be interpreted carefully with contamination differentiated from definitive lung disease, especially as pseudoepidemics of these microorganisms have been well described and attributed to contaminated water supplies, bronchoscopes and hospital laboratories [6–8].

To ensure appropriate diagnosis and treatment, the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) updated their comprehensive guidelines in 2007 [3].

2. Diagnosis

NTM is quite rare and may otherwise be missed unless the physician has a high level of clinical suspicion especially in immunocompromised patients or those with underlying lung disease.

The ATS/IDSA guidelines recommend that patients suspected of NTM lung disease should have an evaluation that consists of at least the following (i) chest radiograph or, in the absence of cavitation, chest HRCT scan; (ii) three or more sputum specimens for AFB analysis; and (iii) exclusion of other disorders such as tuberculosis (TB) and lung malignancy.

Diagnosis can be made without bronchoscopy or lung biopsy in the majority of cases [3].

Abbreviations: AFB, acid fast bacillus; ATS, American Thoracic Society; HAART, highly active antiretroviral therapy; HRCT, high resolution computed tomography; IDSA, Infectious Diseases Society of America; MAC, *Mycobacterium avium* complex; NTM, non-tuberculous mycobacteria; RGM, rapid growing mycobacteria.

* Corresponding author. Tel.: +44 114 2713452; fax: +44 114 2713452.
E-mail addresses: e.mcgrath@sheffield.ac.uk (E.E. McGrath), paul.anderson@sth.nhs.uk (P.B. Anderson).

1094-5539/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pupt.2010.06.002

Once the recommended evaluation has taken place, the physician is in a position to decide on whether the NTM isolate is related to contamination or disease by following the ATS/IDSA guidelines [3] which lay down criteria for the diagnosis of NTM (Fig. 1). The diagnosis of pulmonary infection requires fulfilment of clinical and microbiological criteria. Both are required for diagnosis. Clinically, (i) pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a HRCT scan that shows multifocal bronchiectasis with multiple small nodules along with (ii) appropriate exclusion of other diagnoses are required. Microbiologically only one of the listed criteria are required: positive culture results from at least two separate expectorated sputum samples or positive culture result from at least one bronchial wash or lavage or transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive [3].

3. A therapeutic strategy for the more important lung NTM

Therapy is generally started once the NTM has been identified. Sufficient growth for mycobacterial detection can take up to 6 weeks in the case of slow growing mycobacteria on solid media [9]. Using liquid media, this can be reduced to 1–3 weeks [10]. Once sufficient growth is observed, steps can be taken to differentiate TB from NTM. While traditional analysis including the detection of catalase and niacin production has been useful, advancements including nucleic acid amplification techniques have facilitated rapid and accurate differentiation of the two [11].

Traditionally, once solid media growth is detected, a further 3–6 weeks are required for species identification [12]. Newer techniques including restriction fragment length polymorphism analysis amplification, high performance liquid chromatography and the use of DNA probes and sequencing have led to the rapid identification of each species [13].

Antibiotic susceptibility testing is routinely performed on any isolate that is clinically significant. It is particularly important in *Mycobacterium kansasii* and MAC disease where rifampicin and clarithromycin resistance are tested respectively and if present can mean treatment failure [14]. Susceptibility studies may also help direct alternative regimens in patients who do not respond to empiric therapy or relapse.

The aim of therapy includes an improvement in symptoms, radiology and microbiology although the former 2 can be difficult to demonstrate in patients with severe underlying lung disease. Microbiological improvement is defined as the conversion of sputum positive cultures to negative. Cultures should be performed monthly while on treatment with therapy ceasing once 12 months of negative sputum results have been observed [3]. In the case of MAC disease, symptom improvement is generally expected within 6 months and sputum should convert to negative within 12 months on the recommended regimen [15]. Patients with NTM lung disease that fail to respond to therapy should be investigated for drug resistance or poor compliance [3].

4. *Mycobacterium avium* complex

This organism is the most common non-tuberculous mycobacterial pathogen found in the lung [16]. Lymphadenitis and disseminated disease in the immunocompromised can also occur. Patients may experience night sweats, fatigue, cough, sputum production, haemoptysis and fever. Symptoms may be present for years before a diagnosis is made [17]. MAC commonly causes 2 types of lung disease. The first is fibronodular bronchiectasis, a slowly progressive condition frequently involving the right middle lobe of Caucasian, post menopausal nonsmoking females [17]. HRCT thorax typically demonstrates peripheral peribronchovascular pulmonary nodules and cylindrical bronchiectasis. The more traditional presentation of MAC lung disease is one of apical fibrocavitatory lung disease often found typically in a 40–60 yr old smoking male with a history of alcohol excess [3,18].

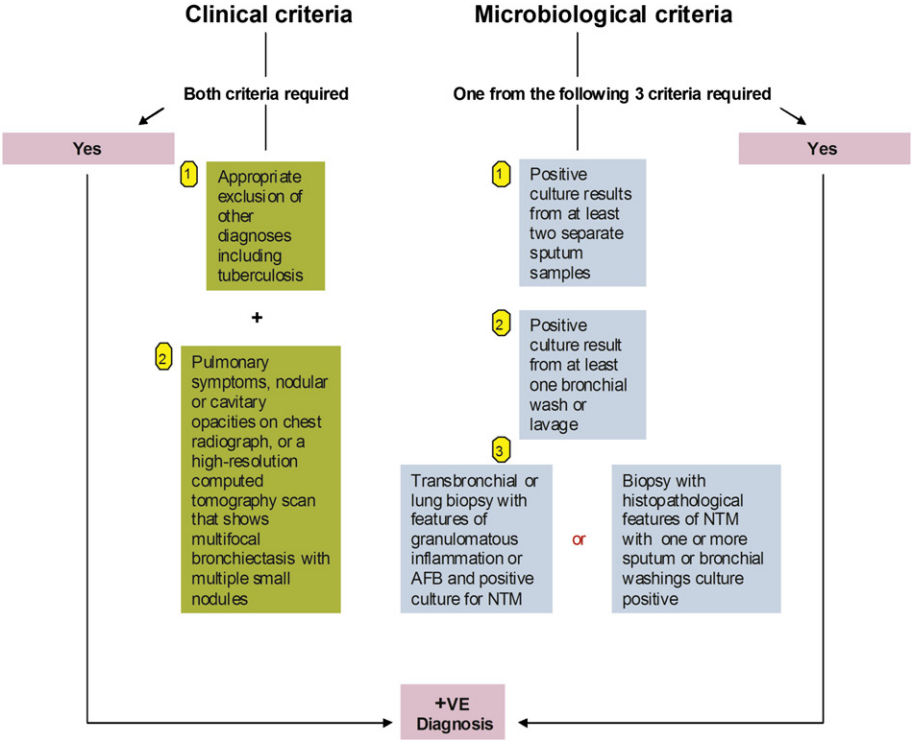

Fig. 1. Recommended criteria for the diagnosis of pulmonary NTM disease [3].