

An update on prevalence of slow-growing mycobacteria and rapid-growing mycobacteria retrieved from hospital water sources in Iran – a systematic review

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Abstract

Introduction This study aimed to assess the prevalence of slow growing mycobacteria (SGM) and rapid-growing mycobacteria (RGM) retrieved from hospital water sources in Iran from 2016 to 2020.

Methods The review was conducted to get eligible published studies from 1st January 2016 to 25th March 2020 based on PRISMA protocol. A combination of related words from the Medical Subject Heading Terms (MeSH), with (AND, OR) were used to search for published studies reporting the prevalence of nontuberculous mycobacteria (NTM) in Scopus, MEDLINE, Web of Sciences, Google Scholar, and Iranian databases. Then data from the studies were extracted and reported.

Results Our study showed that different water sources of hospitals were contaminated with NTMs. The prevalence of RGM isolates in hospital water samples varied between 42.2%–67.5%, and the prevalence of SGM varied between 32.5%–57.7%, respectively. *M. lentiflavum* (84.7%), *M. avium* complex (2.8%–56.4%) and *M. gordonae* (2.8%–56.2%) were the most prevalent NTM species amongst SGM, whereas *M. fortuitum* (2.9%–44.2%), *M. chelonae* (8%–36.8%), *M. mucogenicum* (8%–25.6%) were the most leading NTM isolates among RGM.

Conclusions A high prevalence of NTM was reported from hospital environments particularly hospital water sources which can colonize medical devices, solutions, and water used for patients and cause nosocomial infection. Therefore, the hospitals should check the microbiological quality of the water used.

Keywords Nontuberculous mycobacteria, prevalence, hospital, water resources, environment

Introduction

Nontuberculous mycobacteria (NTMs) are ubiquitous bacteria, naturally living in water including tap water treated with chlorine, shower water, water distribution systems,¹ drinking waters,² soil, dust,³ and aerosol and food substance.⁴ Different nontuberculous mycobacterial species are resistant to most disinfectants and they are also the important contributors to nosocomial infections.⁵ Nowadays, various NTM species have been detected in drinking water with high resistance

against disinfectants such as chlorine.⁶ As well, they can tolerate a varied range of temperature and pH.⁶ Besides, NTMs can also survive in water-flow pipes owing to biofilm formation and hydrophobicity.⁷ Therefore, a wider range of diseases including pneumonitis, asthma, gang ionic infection, pulmonary infection, infection of skin/soft tissue and hypersensitivity specifically in immunocompromised and immunocompetent patients are caused by these microorganisms in humans.⁸ Smoking, pneumoconiosis, chronic obstructive pulmonary diseases, and silicosis are

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the most important predisposing factors for pulmonary infections occurring in immunocompetent patients.⁸ Disseminated infections resulting from NTM, particularly *M. avium* are common in patients with acquired immunodeficiency syndrome (AIDS).⁹

Mycobacterium lentiflavum is one of the slow-growing non-tuberculous mycobacteria that in rare cases cause human diseases. It has been retrieved from young children with cervical lymphadenitis and environmental specimens around the world.¹⁰ Some studies have reported *Mycobacterium fortuitum* in pulmonary involvement, although most of them were case studies. People with underlying diseases such as renal transplantation, malignancy, cystic fibrosis, bronchiectasis,^{11,12} and immunocompromised individuals such as those suffering from AIDS¹³ are more susceptible to *Mycobacterium* lung diseases.

The high colonization of soil and water sources with NTM has unpleasant consequences; affecting the efficacy of BCG vaccine, sensitization with non-tuberculosis mycobacteria prevents the induction of BCG-mediated immune response and decreases the protection against *M. tuberculosis* and presence of NTM.¹⁴ Furthermore, the existence of NTM in water sources, particularly hemodialysis water and potable water, causes colonization of hemodialysis devices and equipment and subsequently NTM will transmit and cause disease in patients who are in hemodialysis units.¹⁵

The colonization of hospital water resources with these bacteria results in subsequent colonization of hemodialysis water, equipment, and devices and naturally the transmission of NTM to patients, especially those hospitalized in hemodialysis and surgery units.¹⁶ Recently, infections owing to NTM have achieved substantial importance owing to their rising prevalence in immunocompromised patients.^{17,18} The main problem with NTM is that some of them, such as *M. simiae*, cause clinically indistinguishable infections from tuberculosis.¹⁹

Reports indicate that most NTMs are inherently resistant to antibiotics used to treat

tuberculosis, which leads to failure in treatment.²⁰ Thus, infection caused by NTMs is mistaken for tuberculosis.^{20,21} There is no single treatment regimen for NTMs, which is due to the spectrum of drug resistance that is affected by the genetic nature of the infecting species.²² Therefore, accurate identification of these species is necessary to apply the best antibiotics.²³ A study from our country reported that 70% of NTMs were resistant to isoniazid, 64% against rifampin. Also, 57%, 35%, 14%, and 7.1% showed resistance against ethambutol, tetracycline, azithromycin and amikacin.²⁴

Although there are few studies about NTM in Iran, considering the importance of the subject and the fact that previous reviews were from the year 2016 and earlier, this study was conducted. Therefore, in this study, we aimed to investigate the combined prevalence of rapid-growing and slow-growing mycobacteria in hospital environments, especially hospital water sources from 2016 to 2020.

Methods

Literature sources and searches

A database was built from published documents reporting the prevalence of nontuberculous mycobacteria including slow-growing mycobacteria (SGM) and rapid-growing mycobacteria (RGM) retrieved from hospital environments. The review was designed based on the protocol for systematic reviews and meta-analysis (PRISMA). A combination of words from the dictionary Medical Subject Heading Terms (MeSH), and Boolean operators (AND, OR) was used for a systematic search of Scopus, MEDLINE, Web of Science, Google Scholar and also, Iranian electronic databases including Scientific Information Database (www.sid.ir), Iranmedex (www.iranmedex.com), Magiran (www.Magiran.com), and Irandoc (www.irandoc.ac.ir) to get eligible published studies from 1st January 2016 to 25th March 2020. The MeSH terms were; “non-tuberculous”, “non-tuberculosis”, “nontuberculous mycobacterium”, “atypical mycobacterium”, “non-tuberculosis mycobacteria”, “NTM”, “MOTT”, “rapid growing mycobacteria”, “RGM”, “slow-growing mycobacteria”, “SGM”, “water sources”, “water

supplies” “environment”, “hospital”, “prevalence”, and “Iran.” The search strategy in PubMed was as follows; (non-tuberculous [MeSH Terms] OR non-tuberculosis [Title/Abstract] OR nontuberculous mycobacterium [MeSH Terms] OR atypical mycobacterium [MeSH Terms] OR non-tuberculosis mycobacteria [MeSH Terms] OR NTM [Title/Abstract] OR MOTT [Title/Abstract]) AND (rapid growing mycobacteria [Title/Abstract] OR RGM [Title/Abstract] OR slow-growing mycobacteria [Title/Abstract] OR SGM [Title/Abstract]), water sources [MeSH Terms] AND water supplies [MeSH Terms] AND (environment [MeSH Terms]) AND (hospital [MeSH Terms]) AND (prevalence [MeSH Terms]) AND (Iran [MeSH Terms]).

Inclusion criteria

Research studies were enrolled if they had the following desired criteria: (i) a study with cross-sectional design, (ii) a study reporting the prevalence of NTM in hospital environments, and (iii) a study reporting a standard method of identifying NTM.

Exclusion criteria

Exclusion criteria were: (i) non-environmental studies; (ii) observational studies with case-control, case reports, case series, randomized controlled trials (RCT), editorials, letters, and studies with cohort design; and (iii) studies that did not provide the outcomes of interest, and studies with no standard method of identifying NTM.

Quality assessment

Included studies were assessed for risk of bias by at least two of the authors using the criteria listed in the Critical Appraisal Skills Programmed checklists (www.casp-uk). Final assessments were achieved according to the agreement between two reviewers.

Data extraction

Descriptive data from selected studies were independently extracted by two separate investigators. Pertinent data included first author, publication time, setting, sample size, NTM

prevalence, source of samples (water, soil, etc.), RGM, SGM, and molecular techniques.

Results

Characteristics of included studies

Initially, 904 records were recognized by searching through relevant databases; after deletion of 409 records due to duplication, the titles of 495 studies were evaluated, and 201 articles were deleted because of irrelevancy. Then, the abstracts of 294 articles were evaluated, and after removing 162 literatures due to irrelevant abstracts, the full-texts of 132 articles were assessed, of which 121 documents were excluded with reasons. Finally, 11 studies were assessed fully for quality. Of these, 5 studies were excluded because of low quality and 6 studies were included in the present systematic review. Studies enrolled from Khuzestan, Razavi Khorasan (Mashhad), East Azerbaijan (Tabriz), Isfahan, and Kermanshah provinces (Table 1). All studies used phenotypic tests for the detection of mycobacteria. These tests included Ziehl-Neelsen (ZN) staining, colony morphology, standard biochemical assays, i.e., growth rate, growth at different temperatures such as 25°C, 32°C, 37°C and 42°C, catalase production, urease activity, tellurite reduction, niacin accumulation, pyrazinamidase, pigment formation, tween opacity, nitrate reduction, and tolerance to 5% NaCl. At last, the isolates were classified into Runyon groups.²⁵ Alongside, molecular techniques were used for differentiation NTM species from TB complex. These included PCR of the *hsp65* gene, and sequence analysis of the 16S *rRNA* gene,^{26,28} PCR RFLP(PRA) *hsp65* gene and sequencing of *rpoB* gene,^{29,30} PCR and sequencing of 16S *rRNA* and *rpoB*,³¹ and *rpoB* gene-PCR(PRA).³²

Overall results

Prevalence of RGM and SGM in hospital water sources

Our study showed that different water sources of hospitals were contaminated with NTMs. The prevalence of RGM isolates in hospital water samples varied between 42.2%–67.5%, and the prevalence of SGM varied

Table 1. Characteristics of studies included in the present meta-analysis

First author	Study time	Publication	Location	Sample size	NTM	Source	Techniques
Azadi ²⁶	2011-12	2016	Isfahan	148	71	Hospital water	PCR <i>hsp65</i> gene sequence of 16S rRNA
Khosravi ²⁹	2013-15	2016	Khuzestan	258	77	Hospital water	(PRA) and <i>rpoB</i> gene sequence
Mohajeri ³¹	2015	2016	Kermanshah	110	35	Drinking water	PCR and sequencing. 16S rRNA and <i>rpoB</i>
Roshdi Maleki ²⁷	2016	2017	Tabriz	120	87	Hospital water	PCR and sequencing <i>hsp65</i> and 16S rRNA
Aryan ³²	-	2018	Mashhad	96	19	Hospital water	<i>rpoB</i> -PCR(PRA)
Moradi ³⁰	2016-17	2019	Tehran	218	85	Hospital water systems	PCR and sequencing of <i>hsp65</i> and <i>rpoB</i>

between 32.5%–57.7%, respectively.

Subgroup analysis for the prevalence of RGM and SGM isolates

As abstracted in Table 2, *M. lentiflavum* (84.7%), *M. avium* complex (2.8% - 56.4%) and *M. gordonae* (2.8% - 56.3%) were the most prevalent NTM species amongst slow growing mycobacteria (SGM), whereas *M. fortuitum* (2.9%–44.2%), *M. chelonae* (8%–36.8%), *M. mucogenicum* (8%–25.6%), were the leading NTM isolates among RGM. Other data on the prevalence rate of SGM and RGM are listed in Table 2.

Discussion

The prevalence of RGM isolates in hospital water samples varied between 42.2% and 67.5%, and the prevalence of SGM varied between 32.5% and 57.7%, respectively. This difference in the prevalence of NTM in Iran is possibly referred to the difference in geographical location, type of diagnostic method (phenotypic or molecular), weather condition, and use of different decontamination techniques.³³ In agreement with our study, a prior systematic review and meta-analysis from Iran reported the pooled prevalence of 38.3% in environmental samples.¹⁶ Similar with our findings, Covert et al. isolated different species of NTMs, 54% from ice samples and 35% from public drinking water sources.³⁴ Also, in accordance with our results,

studies from Turkey,³⁵ Germany,³⁶ Czech Republic,³⁷ and China³⁸ indicated the NTM prevalence about 20.6%, 57%, 46.7%, and 20.4% from hospital water samples, respectively. Although the prevalence of NTMs is approximately the same between the mentioned studies and the present review, the periods of time for collection, the regions, methods of identification, and likely the water quality values are different.³³

In the present review, *M. lentiflavum* (84.7%), *M. avium* complex (2.8%–56.4%) and *M. gordonae* (2.8%–56.3%) were the most prevalent NTM species amongst SGM, whereas *M. fortuitum* (2.9%–44.2%), *M. chelonae* (8%–36.8%), *M. mucogenicum* (8%–25.6%), were the leading NTM isolates among RGM. A study from Australia has reported that species of *M. abscessus*, *M. lentiflavum*, and *M. kansasii* retrieved from potable water distribution systems are highly connected or equal to those shown in human infections.³⁹ Reports confirmed that principally chronic infection with *M. abscessus* is related with deteriorating lung function during time in patients with cystic fibrosis.⁴⁰ Furthermore, *M. abscessus* complex causes disease in nearly all human tissues.⁴¹ *M. abscessus* complex are more difficult to treat because of antimicrobial drug resistance.^{5,41,42}

Table 2. Prevalence of both RGM and SGM in the present review

NTM	Prevalence of NTMs (%)					
	Azadi	Khosravi	Mohajeri	Roshdi maleki	Aryan	Moradi
<i>M. simiae</i>	7	3.910		20.831	15.821	
<i>M. paragordoniae</i>	21.111			6.251		2.321
<i>M. gordonae</i>	2.811	16.810	5	56.251	15.821	13
<i>M. avium complex</i>		56.410	2.810			
<i>M. intracellulare</i>			2.810			
<i>M. lentiflavum</i>	28.100					84.710
<i>M. kansasii</i>				14.58		
<i>M. marinum</i>				2.091		
<i>M. fortuitum</i>	2.883	44.145		23.081	10.511	
<i>M. abscessus</i>				17.951		
<i>M. chelonae</i>			8	12.821	36.812	
<i>M. peregrinum</i>		5.20	8	7.711		
<i>M. mucogenicum</i>			8	25.641		
<i>M. novocastrense</i>	7			2.561		
<i>M. austroafricanum</i>	1.412				10.511	
<i>M. fredriksbergense</i>	9.851					
<i>M. canariensis</i>	5.624					
<i>M. setense</i>	4.213					
<i>M. obuense</i>	1.412					
<i>M. phocaicum-like</i>	1.412		8.5	10.251		
<i>M. senegalense</i>		7.721				
<i>M. iranica</i>		1.301	2.811			
<i>M. goodii</i>			11.512			
<i>M. aurum</i>			11.512			
<i>M. gastri</i>			11.512			
<i>M. porcinum</i>			8			
<i>M. massiliense</i>			5			
RGM	42.210	67.532		44.831		
SGM	57.713	32.467		55.171		

As well, *M. abscessus* complex can cause infection in postsurgical and postprocedural wounds due to its resistance against disinfectants, antimicrobial and antibiotic agents.^{41,42} Inconsistent with current findings, in a study conducted by Torvinen et al. in 2004, more than 90% of mycobacterial isolates were *M. lentiflavum* and *M. gordonae*.⁴³ Similarly, a study from South Korea reported a prevalence of 65% for *M. lentiflavum* in drinking water samples.⁴⁴ Also, similar to our findings, in Turkey, Genc et al. reported *M. lentiflavum* and *M. gordonae* as the highest SGM from hospital water samples.³⁵ *M. gordonae* is largely isolated from water resources because it has a limited need for nutrition and a high resistance and tolerance up to 330 times more than *E. coli* against chlorine.⁶ Accordingly,

Shin et al. (2007) reported a high prevalence (73.3%) of *M. gordonae*⁴⁵ compared to our study that showed the importance of this microorganism in water systems. Similar to our study, other studies reported *M. fortuitum*, *M. chelonae*, and *M. abscessus* as the most common RGM, which are often related to postsurgical or posttraumatic infections, localized infections of the skin and subcutaneous tissue.^{20,46} A common trait of these infections is exposure to colonized water sources.⁴⁶ Therefore, control of water sources is especially important when water is used specifically for dialysis patients.

In our study the second most prevalent RGM belonged to *M. chelonae* (12.2%); *M. chelonae* is possibly the most predominant NTM accountable for skin and soft tissue infections.⁴⁷ A study

carried out by Carson and et al. on water samples collected from the faucet, found that *M. chelonae* strains were capable of proliferation in distilled water systems with marked resistance against chlorine.⁴⁸ The incidence of comparable NTM profiles, with *M. chelonae* as the highest NTM species in tap water samples and from patients with subcutaneous abscesses endorses this environmental source.⁴⁹ It should be taken into consideration that infections produced by *M. abscessus* commonly occur in people with genetic defects, immunosuppression, and chronic pulmonary diseases.⁵⁰

High rates of NTM colonization have been reported in older drinking water pipe systems,⁵¹ although less recent colonization has been reported in newly built water systems.⁵² High rates of colonization have been reported in hospital drinking water systems, dialysis wards, and dental offices, with varied prevalence rates ranging from 60% to 100%.⁵³⁻⁵⁵

Therefore, the application of methods including high chlorine concentrations, UV irradiation, hot water, or disinfection of potable water with copper silver ion-generation system could minimize the risk for NTM diseases in hospitalized patients.^{7,56}

In summary, in this study, we showed that the presence of different types of NTM in hospital water sources is high. Although our data extracted from the studies included did not show any special differences in the prevalence of NTMs from 2016 until 2020 in different regions of Iran, colonization of hospital water supplies with NTM possibly can lead to nosocomial infection.

Thus, tap water and other hospital water sources should be inspected for the presence of NTM to avoid hospital-acquired infection, also, water filtration is preferable in cases used for immunocompromised patients.³⁸

Conclusions

In this review, a high rate of NTM (both RGM and SGM) was reported, which through these water supplies can colonize medical devices, solutions, and water used especially for dialysis patients and cause nosocomial infection. Therefore, the hospital should check the

microbiological quality of the water used particularly in critical wards, equipment and devices. It is also advisable to filter the water used for dialysis and immunocompromised patients.

Authors' contributions statement: MA designed the study, wrote the protocol, the first draft of the manuscript and revised the final draft of the manuscript. PK and AK have contributed to search and performing the statistical analysis. All authors read and approved the final version of the manuscript.

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