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Review Article

Mycobacterium chimaera infections: An update

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ABSTRACT

Mycobacterium chimaera is a non-tuberculous mycobacterium belonging to the *Mycobacterium avium* complex, described for the first time in 2004. It acts as an opportunistic pathogen, with infections, usually respiratory illnesses, occurring more frequently in immunocompromised patients or in patients with underlying respiratory diseases. During the last decade *Mycobacterium chimaera* disseminated infections following cardiothoracic surgery, especially open-heart surgery, have been increasingly reported worldwide. From a pathogenic standpoint, *Mycobacterium chimaera* is acquired during cardiopulmonary bypass via bioaerosols emitted from contaminated heater-cooler units water systems. Due to non-specific symptoms and long latency, postoperative *Mycobacterium chimaera* infections may not be promptly diagnosed and treated, and may become life-threatening. The indication for revision surgery needs to be carefully evaluated on a case-by-case basis, and antibiotic therapy should be based on drug susceptibility testing results. Our review aims to provide an updated account of microbiological characteristics, clinical presentation, diagnosis, and management of *Mycobacterium chimaera* infections, with a special focus on those developing after cardiothoracic surgery.

Contents

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1. Introduction

Mycobacterium chimaera is a ubiquitous water-borne non-tuberculous mycobacterium belonging to the *Mycobacterium avium* complex (MAC), first described by Tortoli et al. in 2004 [1]. The name "chimaera", referring to the mythological creature consisting of parts from three different animals, is justified by the mix of genetic features characterizing *Mycobacterium chimaera*'s strains; in fact, at its first identification, even if genetically different from *M. avium*, *M. intracellulare*, or *M. scrofulaceum*, reverse hybridization–based line probe assay suggested that the strain belonged to MAC, being closely related to the three other species [2].

M. chimaera acts as an opportunistic pathogen, and respiratory infections may develop through inhalation of aerosolized particles containing the pathogen, usually in immunocompromised patients or in patients with underlying respiratory diseases [3,4].

In 2013, Achermann et al. [5] described the first cases of *M. chimaera* infections following cardiothoracic surgery, especially open-heart surgery, resulting in cardiac complications (prosthetic valve endocarditis), surgical site infections, vascular graft infections or disseminated disease that could occur even after a latent period of months to years (range 3–72 months) [6,7]. The first cases were reported in Switzerland, but the phenomenon is now of global relevance, reasonably because of both an increase in the use of extracorporeal membrane oxygenation (ECMO) systems (which predispose to *M. chimaera* acquisition, see below) and a higher capability to identify *M. chimaera* and distinguish it from other MAC bacteria in the microbiological laboratory [5,8]. Signs, symptoms and laboratory features are often non-specific, and include low-grade fever, fatigue and dyspnoea [9]. If not promptly diagnosed and properly treated, *M. chimaera* infections my become life-threatening [10,11].

The primary mode of transmission has been identified in the water tanks of heater-cooler units (HCUs), thermoregulatory components of ECMOs, which produce a contaminated aerosol [12–14] (Fig. 1). Stagnation of water and high temperature (up to 40 °C) promote the formation of biofilms, creating a more favourable environment for *M. chimaera* [15,16]. Patients treated with ECMO for open-heart surgery are more exposed to *M. chimaera* infections than patients treated with ECMO for respiratory failure due to larger potential entry sites for the pathogen [12].

Currently no standardized treatment for *M. chimaera* infection after open-heart surgery exists. Revision surgery has to be evaluated on a case-by-case basis and antibiotic therapy includes drugs used for more common strains of the MAC. Ideally, antibiotic therapy should be guided by the results of a drug susceptibility test performed in a reference centre for mycobacterial pathogens [9].

Our manuscript aims to review microbiological and clinical characteristics (including presentation, diagnosis, and management) of *M. chimaera* infections, with a special focus on those developing after cardiothoracic surgery.

2. Methods

On January 04, 2019 we performed a MEDLINE/PubMed search. The complete search string was as follows: (Mycobacterium chimaera) AND ("January 01, 1990" [Date - Publication]: "3000" [Date - Publication]). Of the 204 papers identified, 122 were excluded by title and abstract screening. The full texts of the remaining 82 papers and of pertinent references were then retrieved and collectively discussed, with the decision about inclusion in the present narrative review being ultimately made according to the subjective impression of the authors. Eventually, the review was organized in the following paragraphs: (i) "microbiological characteristics and identification"; (ii) "clinical presentation and diagnosis of *M. chimaera* infections"; (iii) "drug susceptibility testing"; (iv) "treatment of *M. chimaera* infections"; (v) "public health issues".

3. Microbiological characteristics and identification

M. chimaera, as part of the NTM family, is a ubiquitous - environmental mycobacteria, especially linked to natural waters sources and building water distribution systems; however, in Europe, its prevalence in the environment is mostly unknown [17–19]. It is a slow-growing, non-pigmented, acid-fast positive, mycobacterium distinguished by non-motile and non-spore forming coccobacilli [1]. The highly lipophilic cell wall, the low number of porins associated with a variety of efflux pumps and inducible resistance mechanisms confer a resistant cell wall and natural drug resistance to *M. chimaera* as well as to the other MAC group [1,17,20,21].

As slow-growing mycobacteria, *M. chimaera* 's samples from patient and environmental can take up to 6–8 weeks to culture [16]. All the samples can be processed in a mycobacteriology laboratory with biosafety containment level 2 [22,23]. Ideally, identification of *M. chimaera* should be performed at mycobacterial reference laboratories. DNA sequencing can be performed in any invasive sample (e.g. blood, pus, tissue biopsy or implanted prosthetic devices/material). The European Union (EU) protocol for laboratory diagnosis and environmental testing of *M. chimaera* provides quality information for processing and culturing of different types of environmental samples (e.g. water and/or air samples) [22,23].

M. chimaera grows slowly at temperatures in the range of 25–35 °C; the colonies are scotochromogenic and rough. Commonly performed biochemical tests are negative with the only exception of Tween 80 hydrolysis, which may be variable. Lowenstein–Jensen containing 5% NaCl inhibits the growth of *M. chimaera*. Regarding liquid culture, MGIT performed better then solid culture, showing a lower detection limit for *M. chimaera* [13]. According to MALDI-TOF MS identification, *M. chimaera* is phylogenetically close to *M. simiae* and *M. avium*. Identification through the gene sequencing of internal transcribed spacer (ITS) 16–23S is

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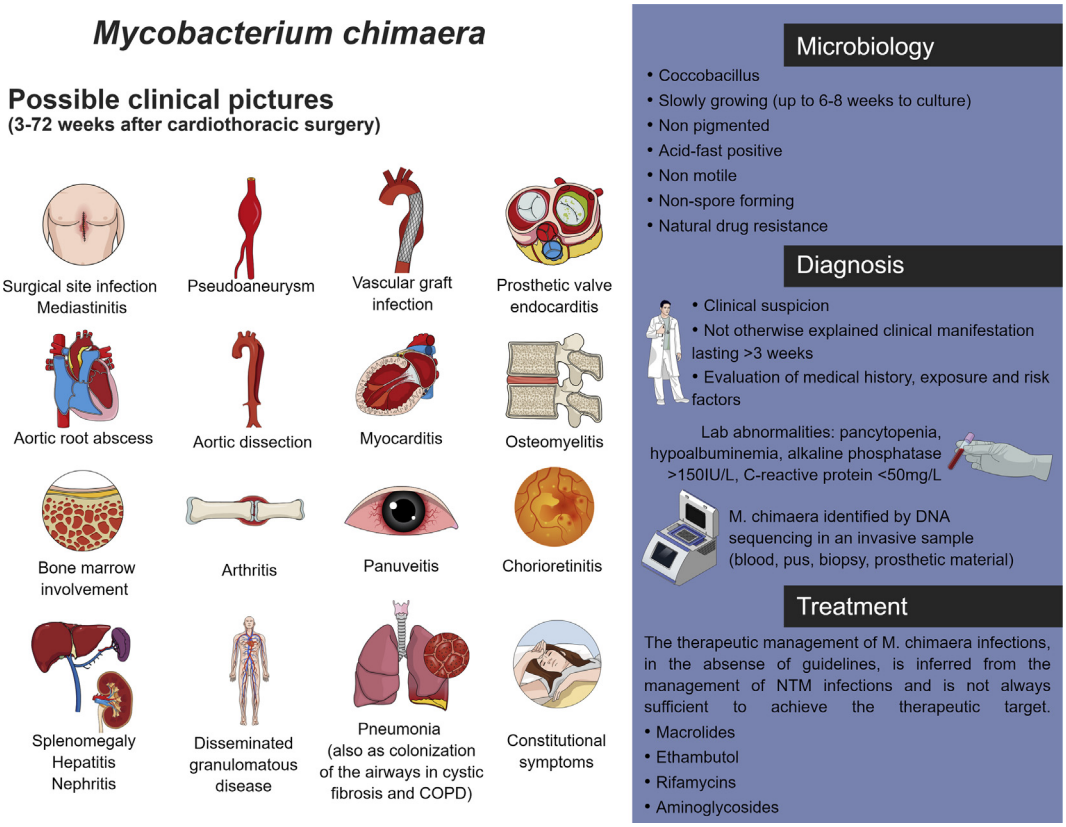

Fig. 1. Possible clinical pictures of *Mycobacterium chimaera*.

an effective method to discriminate M. chimaera among closely related mycobacteria. Currently, differentiation of *M. chimaera* requires gene sequencing of the 16–23S ITS region and, high performance liquid chromatography (HPLC) profile [1,20]. In 2016, the genome of *M. chimaera* has been completely sequenced, showing 6.33 megabase pair, with a guanine + citosyne content of 67.56% and encoding for 4926 protein-coding genes, as well as 74 tRNAs, one ncRNA, and three rRNA genes [21]. Whole-genome sequencing (WGS) applied for phylogenetic comparison and infection control purposes is considered effective and appropriated. Other molecular kits, such as GenoType Mycobacterium CM, INNO-LiPA Mycobacteria and MALDI-TOF with 16S rRNA gene-sequencing or RAPD-PCR have been used to detect *M. chimaera* [7,9,11].

4. Clinical presentation and diagnosis of *M. chimaera* infections

4.1. Pulmonary disease

Pneumonia caused by *M. chimaera* can result as a consequence of colonization of the airways in immunocompromised patients or in patients with underlying chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease (COPD), bronchiectasis and cystic fibrosis) [24–26] (Fig. 1). However, although MAC strains are frequent colonizers in cystic fibrosis and COPD patients, to define the real pathogenic role of MAC, the Thoracic Society (ATS) criteria for MAC lung disease need to be fulfilled [27]. Pulmonary and systemic symptoms can mimic tuberculosis (fever or low-grade fever, cough, haemoptysis, night sweats, weight loss, dyspnoea and chest pain) [28]. In the suspect of *M. chimaera* pulmonary disease, at least two samples from sputum (or one from bronchoalveolar lavage) for Acid-Fast Stain (AFS) and for culture should be collected; imaging with chest-X-ray and/or chest computed tomography is advised for diagnosis (consolidation, excavations, necrotizing pneumonia are all findings related to *Mycobacterium chimaera* pulmonary disease) and follow-up [25,26,28,29]. Because of similar radiological pattern with active TB, attention should be focused on TB medical history (e.g. previous contact, epidemiology) and on prompt molecular identification of positive acid-fast bacilli samples. Of note, a low body mass index has also been associated with *M. chimaera* infection [30].

4.2. Extrapulmonary manifestation

4.2.1. Infection after cardiothoracic surgery

M. chimaera is distinguished from the other MAC species by its propensity to cause post-cardiothoracic surgery infections. The epidemic of *M. chimaera* in cardiac surgery patients started through airborne transmission by contaminated water tanks used in heater-cooler devices (Stockert-LivaNova-Sorin 3T), which regulate patients' body temperature during cardiac surgery [31] (Fig. 2). In 2015, in Pennsylvania, three patients were infected from a single heating and cooling unit in the same hospital facility, thus providing further evidence that strengthened the association between the heater-cooler units and *M. chimaera* [31,32]. Prosthetic valve endocarditis, vascular graft infection, surgical site infection, disseminated mycobacterial infection, arthritis, osteomyelitis and bone marrow involvement, even with haemophagocytic lymphohistiocytosis, have all be documented as possible consequences of *M. chimaera* infection after open heart cardiac surgery requiring extracorporeal circulation, due to the use of contaminated heater-cooler units [5,27,33,34]. Incubation period after exposure to *M. chimaera* is long, with a median of 17 months (range 3–72

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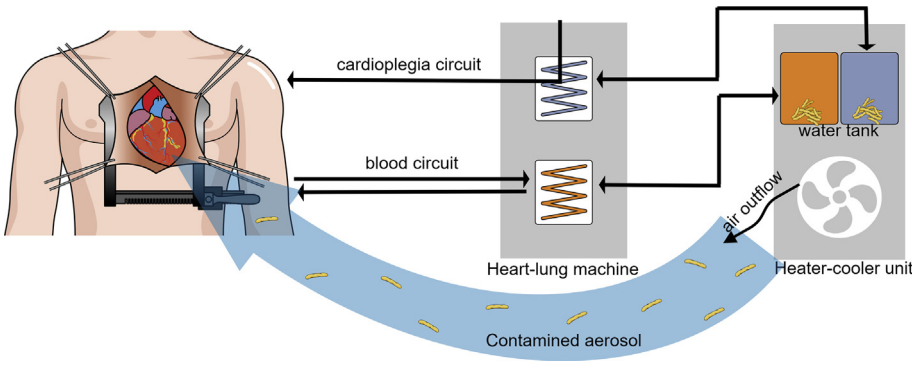

Fig. 2. Instrumental investigation.

months) and a median time to diagnosis of 26 months (range 5–60 months) after surgery [35].

In general, instrumental investigations should be focused in consideration of the presumably involved organ. If a disseminated or post-surgical infection is suspected, instrumental investigation should be broadened to exclude chorioretinitis (i.e.: fundoscopic exam), endocarditis (transesophageal echocardiogram), or clinically silent localizations (PET/CT scan and radiolabeled leukocyte scintigraphy) [23]. Finally, in Europe the diagnosis of confirmed and probable *M. chimaera* infections potentially associated with heater-cooler units is standardized using clinical and exposure criteria in association with microbiological, histopathological and molecular findings.

In the following paragraphs, we provide a brief description of the different clinical pictures of *M. chimaera* infections after cardiothoracic surgery, while diagnostic criteria are summarized in Table 1.

4.2.2. Prosthetic valve endocarditis

Definition of *M. chimaera*'s endocarditis on prosthetic valve includes positive cultures or molecular methods on heart valves with echocardiographic and/or histopathological signs of infection [36]. Symptoms associated with *M. chimaera*'s endocarditis are fatigue, low-grade fever, hepatitis, renal insufficiency and splenomegaly. In a recent case series from UK, the following laboratories abnormalities were noted: pancytopenia, hypoalbuminemia, alkaline phosphatase >150 IU/L, a C-reactive protein less than 50 mg/L [6].

4.2.3. Vascular graft infection and surgical site infection

Virtually any vascular graft can be infected by *M. chimaera*, however aortic pseudoaneurysm, aortic dissection and root abscess can be seen as consequences of post-open heart cardiac surgery with the use of contaminated heater-cooler units [34,37,38]. As in the other localization of *M. chimaera*, symptoms are mostly non-specific: low-grade fever, shortness of breath and night sweats can be present [34,37]. Inflamed tissue involving the vascular-graft, with abscess, can be seen intra-operatively; intra-operative specimens from the infected graft, or from sternal wounds in case of deep surgical site infection, should be promptly sent for culture [37].

4.2.4. Osteomyelitis

Chronic localized pain, purulent discharge from cutaneous fistula and the above-mentioned unspecific symptoms may correlate to *M. chimaera* osteomyelitis [39]. Positive medical history and a bone biopsy with culture are helpful for diagnosis. Vertebral osteomyelitis caused by MAC or other NTM may lead to neurologic deficits, spinal instability due to possible anti-mycobacterial treatment failure and need close monitoring with

Table 1
Case definition of M. chimaera infections potentially associated with heater-cooler units.

CLINICAL CRITERIA
Any of the following:

- Prosthetic valve endocarditis
- Prosthetic vascular graft infection
- Sternotomy wound infection
- Mediastinitis
- Manifestation of disseminated infection including embolic and immunologic manifestations, e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis, myocarditis.

EXPOSURE CRITERIA
Surgery requiring cardiopulmonary bypass in the five years prior to the onset of symptoms of infection.

CONFIRMED CASE
Clinical + exposure criteria + M. chimaera detected and identified by DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

PROBABLE CASE

- Clinical + exposure criteria + M. chimaera detected by direct PCR and amplified DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)
- Clinical + exposure criteria + MAC detected by culture or direct PCR from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)
- Clinical + exposure criteria + histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid-fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound.

MAC = *Mycobacterium avium* complex.
PCR = Polymerase chain reaction.
Adapted from 2015 ECDC case definition [22].

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multidisciplinary approach (e.g. infectious diseases specialist, neuro-surgeon, orthopaedics and microbiologist)

4.2.5. Disseminated granulomatous disease

Due to the non-specific symptoms, such as fatigue, weight loss, cough, and low-grade fever, and the possibility of ocular involvement, *M. chimaera* infections may be mis-diagnosed as sarcoidosis [6]. Moreover, histopathological findings with of granulomatous lesions may support a presumptive diagnosis of sarcoidosis [6,40]. In a case series from United States (US), two out of three patients with *M. chimaera* infection had ocular involvement and were mis-diagnosed as sarcoidosis [40]. In 2019 three cases of fatal granulomatous encephalitis caused by M. chimaera disseminated infection were reported in Canada after cardiac surgery. They presented as non-specific neurocognitive decline and the diagnosis was delayed according to the time required by microbiological detection [41]. Careful staining of the histopathological samples for mycobacterial pathogens (e.g. uramine-phenol staining rather than the Ziehl-Neelsen method due to enhanced sensitivity) may help the diagnosis [39]. Of note, steroids treatment, first line therapy for sarcoidosis, could worsen *M. chimaera* infection.

5. Drug susceptibility testing

The clinical utility of drug susceptibility testing (DST) is the correlation between *in vitro* and *in vivo* susceptibility to a determinate drug. Therefore, breakpoint concentration should aid to predict outcome of treatment [33]. In 2011, the second set of recommendations for antimicrobial susceptibility testing (AST) by Clinical and Laboratory Standards Institute (CLSI) has been published, suggesting for MAC isolates that AST should be performed in broth by either the microdilution or macrodilution method (with the macrodilution 12B method as the preferred choice) [33,36]. Moreover, special care should be taken to select transparent colonies for testing [36,37]. Macrolides are the pivot of *M. chimaera*'s treatment and only macrolide susceptibility testing is advised [36,37]. In a recent study by Maurer et al., out of 202 strains of *M. chimaera*, just 1% was resistance to clarithromycin [38]. Resistance to macrolides has been defined as clarithromycin MICs of $\geq$64 μg/ml at pH 6.8, a MIC of $\geq$32 μg/ml at pH 7.3 to 7.4. Intermediate MICs (16–32 μg/ml, on the base of media pH) may suggest a mixed population of MAC strains and should be confirmed [36,38]. Indeed, patients with intermediate clarithromycin MICs should be carefully monitored with repeat cultures for the possibility of emerging macrolide resistance [37]. Again, in the study by Maurer et al., the rifabutin epidemiological cut-off (ECOFF) for *M. chimaera* was 2 mg/L, one dilution above the other MAC strain tested in the study, while for streptomycin the tentative ECOFF was 64 mg/L [38]. Currently, clinical breakpoints by CLSI are available only for clarithromycin, moxifloxacin and linezolid, whereas there is no available information about clofazimine's breakpoint [39].

6. Treatment of *M. chimaera* infections

6.1. Treatment of pulmonary diseases

Outcomes of *M. chimaera* lung infections are comparable to those of MAC lung infections and, lacking specific guidelines recommendation regarding the treatment of infection caused by this microorganism, its therapeutic management is inferred from the management of MAC infections [36,41,42]. Therefore, the cornerstone of *M. chimaera* infections is a combination of a rifamycin with a macrolide and ethambutol for at least 12 months (after sputum conversion in case of lung disease). This combination is modified according to the clinical and radiological severity of the disease, macrolide sensitivity and HIV co-infection [36,41]. Mandatory it is to obtain a sensitivity test for macrolides to further investigate other possible resistance patterns and to set up an effective treatment. Despite an *in vitro* effective antimicrobial therapy, mortality in *M. chimaera* infections remains high (50–60%) [7,9,10] and a prolonged treatment is associated with adverse reactions and cumulated toxicity. In fact, a long-term macrolide based treatment yields the possibility of QTc prolongation, hepatic failure and colitis due *Clostridioides difficile* [43].

6.2. Treatment of extrapulmonary diseases

No differences of treatment regimen are indicated between pulmonary and extra-pulmonary infection. Survival is enhanced with surgical debridement of infected lesions; the duration of treatment (as well as the definition of culture conversion) is still not well established for extrapulmonary diseases, although a minimum of 12 months of treatment are considered necessary in *M. chimaera* endocarditis. Overall, the duration of treatment for extrapulmonary forms needs to be tailored on a case-by-case basis, according to the subjective and objective responses to treatment [9,10,33,44].

Notably, in their retrospective analysis of prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery, Kohler et al. demonstrated that target serum drug concentrations were not achieved in the majority of patients [9]. For instance, serum concentration of clarithromycin, ethambutol, rifabutin achieved the therapeutic target only in 44%, 37%, 52% of measurements, respectively, despite the application of antibiotic dosages (clarithromycin 500 mg every 12 h, ethambutol 15–25 mg/kg/day, rifabutin 150 mg every 12 h). In this regard, it has been proposed that clarithromycin concentration in tissues and alveolar macrophages may be higher than in blood, possibly ensuring full activity against the target organism as recommended by current NTM guidelines despite sub-therapeutic blood concentrations [36,41]. Of note, there could also be a potential role in the treatment of *M. chimaera*, always as part of combination regimens, for bedaquiline, amikacin, meropenem + clavulanic acid, and linezolid, deserving further investigation [38,45–47].

7. Public health issues

Infections due to NTM not related to cardiothoracic surgery are not generally considered a public health issue. However, healthcare–associated transmission of NTM infections and healthcare–associated hypersensitivity lung disease from indoor stagnant water sources, as well as surgical procedures where exposure to NTM contaminated liquid is addressed, need to be investigated to avoid further spreading of the disease [48]. A general recommendation is to avoid tap water or ice derived from tap water during the manipulation of intravenous catheter and endoscopes or their employment in the operating room, especially during cardiac surgery, and also during mammoplasty because of the report of infections due to other mycobacterial species related to *M. chimaera* [36,49].

Careful checking of tap water and/or operating room devices, through periodic sampling, may be help preventing further contaminations and possible infections.

In case of infections potentially associated with HCUs after cardiothoracic surgery, public healthcare recommendations are different. A mitigation strategy requires separating the operative room from the HCU exhaust bioaerosol [50]. Having been associated with LivaNova/Sorin HCUs (but the potential link with other brands HCUs has not been excluded yet), interim United States Food and Drug Administration recommendations are aimed mainly for

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3T Stockert-LivaNova-Sorin devices users with updates recently published online, including advices in order to avoid the potential growth of NTMs and other organisms in the water tanks of any HCUs devices [51].

8. Conclusion

To reduce morbidity and mortality due to *Mycobacterium chimaera*, high-level of awareness, enhanced decontamination strategies as well as isolation of the heater-cooler units from the operating room and proper antimycobacterial treatment are required; moreover, regular testing of machines and water sampling and re-design of water circulation systems should be implemented in order to decrease the risk of infection.

Transparency declarations

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Declaration of Competing Interest

The Authors declare no conflict of interests.

References

[1] Tortoli E, Rindi L, Garcia MJ, Chiaradonna P, Dei R, Garzelli C, et al. Proposal to elevate the genetic variant MAC-A, included in the *Mycobacterium avium* complex, to species rank as *Mycobacterium chimaera* sp. nov. Int J Syst Evol Microbiol 2004;54:1277–85.
[2] Henry R. Etymologia: Mycobacterium chimaera. Emerg Infect Dis 2017;23(3):499.
[3] Zheng C, Fanta CH. Non-tuberculous mycobacterial pulmonary infection in the immunocompetent host. QJM 2013 Apr;106(4):307–15.
[4] Honda JR, Hasan NA, Davidson RM, Williams MD, Epperson LE, Reynolds PR, et al. Environmental nontuberculous mycobacteria in the Hawaiian Islands. PLoS Negl Trop Dis 2016 Oct 25;10(10):e0005068.
[5] Achermann Y, Rossle M, Hoffmann M, Deggim V, Kuster S, Zimmermann DR, et al. Prosthetic valve endocarditis and bloodstream infection due to *Mycobacterium chimaera*. J Clin Microbiol 2013;51:1769–73.
[6] Dalvi S, Das P. Prosthetic heart valve surgery and potential risk of developing *Mycobacterium chimaera* endocarditis. Clin Med 2018 Aug;18(4):301–3.
[7] Ninh A, Weiner M, Goldberg A. Healthcare-associated *Mycobacterium chimaera* infection subsequent to heater-cooler device exposure during cardiac surgery. J Cardiothorac Vasc Anesth 2017 Oct;31(5):1831–5.
[8] Ortiz-Martinez Y, Galindo-Regino C, González-Hurtado MR, Vanegas-Pastrana JJ, Valdes-Villegas F. State of the art on *Mycobacterium chimaera* research: a bibliometric analysis. J Hosp Infect 2018 Nov;100(3). e159-e160.
[9] Kohler P, Kuster SP, Bloemberg G, Schulthess B, Frank M, Tanner FC, et al. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery. Eur Heart J 2015 Oct 21;36(40):2745–53.
[10] Scriven JE, Scobie A, Verlander NQ, Houston A, Collyns T, Cajic V, et al. Mycobacterium chimaera infection following cardiac surgery in the United Kingdom: clinical features and outcome of the first 30 cases. Clin Microbiol Infect 2018 Nov;24(11):1164–70.
[11] Lecorche E, Haenn S, Mougari F, Kumanski S, Veziris N, Benmansour H, et al. Comparison of methods available for the identification of *Mycobacterium chimaera*. Clin Microbiol Infect 2018 Apr;24(4):409–13.
[12] Garvey MI, Phillips N, Bradley CW, Holden E. Decontamination of an extracorporeal membrane oxygenator contaminated with *Mycobacterium chimaera*. Infect Control Hosp Epidemiol 2017 Oct;38(10):1244–6.
[13] Schreiber PW, Köhler N, Cervera R, Hasse B, Sax H, Keller PM. Detection limit of *Mycobacterium chimaera* in water samples for monitoring medical device safety: insights from a pilot experimental series. J Hosp Infect 2018 Jul;99(3):284–9.
[14] Götting T, Klassen S, Jonas D, Benk Ch, Serr A, Wagner D, et al. Heater-cooler units: contamination of crucial devices in cardiothoracic surgery. J Hosp Infect 2016 Jul;93(3):223–8.
[15] Department of Health. Health technical memorandum (HTM) 04- 01: safe water in healthcare premises. Available at: https://www.gov.uk/government/publications/hot-and-coldwater-supply-storage-and-distribution-systems-for-healthcarepremises. [Accessed February 2017].
[16] Walker J, Moore G, Collins S, Parks S, Garvey MI, Lamagni T, et al. Microbiological problems and biofilms associated with *Mycobacterium chimaera* in heater-cooler units used for cardiopulmonary bypass. J Hosp Infect 2017 Jul;96(3):209–20.
[17] Wallace Jr RJ, Iakhiaeva E, Williams MD, Brown-Elliott BA, Vasireddy S, Vasireddy R, et al. Absence of Mycobacterium intracellulare and presence of Mycobacterium chimaera in household water and biofilm samples of patients in the United States with Mycobacterium avium complex respiratory disease. J Clin Microbiol 2013 Jun;51(6):1747–52.
[18] Falkinham 3rd JO. Ecology of nontuberculous mycobacteria-where do human infections come from? Semin Respir Crit Care Med 2013 Feb;34(1):95–102.
[19] van der Wielen PW, Heijnen L, van der Kooij D. Pyrosequence analysis of the hsp65 genes of nontuberculous mycobacterium communities in unchlorinated drinking water in The Netherlands. Appl Environ Microbiol 2013 Oct;79(19):6160–6.
[20] Frothingham R, Wilson KH. Sequence-based differentiation of strains in the Mycobacterium avium complex. J Bacteriol 1993;175:2818–25.
[21] Hasan NA, Honda JR, Davidson RM, Epperson LE, Bankowski MJ, Chan ED, et al. Complete genome sequence of Mycobacterium chimaera strain AH16. Genome Announc 2016 Nov 23;4(6). e01276-16.
[22] European Centre for Disease Prevention and Control. EU protocol for case detection, laboratory diagnosis and environmental testing of Mycobacterium chimaera infections potentially associated with heater-cooler units: case definition and environmental testing methodology. Stockholm: ECDC; 2015.
[23] Thomson R, Carter R, Gilpin C, Coulter C, Hargreaves M. Comparison of methods for processing drinking water samples for the isolation of Mycobacterium avium and Mycobacterium intracellulare. Appl Environ Microbiol 2008 May 15;74(10):3094–8.
[24] Larcher R, Lounnas M, Dumont Y, Michon A-R, Bonzon L, Chiron R, et al. Mycobacterium chimaera pulmonary disease in cystic fibrosis patients, France, 2010–2017. Emerg Infect Dis 2019 Mar;25(3):611–3.
[25] Cohen-Bacrie S, David M, Stremler N, Dubus JC, Rolain JM, Drancourt M. Mycobacterium chimaera pulmonary infection complicating cystic fibrosis: a case report. J Med Case Rep 2011 Sep 22;5:473.
[26] Schweickert B, Goldenberg O, Richter E, Göbel UB, Petrich A, Buchholz P, et al. Occurrence and clinical relevance of Mycobacterium chimaera sp. nov., Germany. Emerg Infect Dis 2008;14:1443–6.
[27] Butterworth J. Mycobacterium chimaera associated haemophagocytic lymphohistiocytosis. Open J Blood Dis 2016;6:53–8.
[28] Liu G, Chen ST, Yu X, Li YX, Ling Y, Dong LL, et al. Bacteriological and virulence study of a Mycobacterium chimaera isolate from a patient in China. Antonie Leeuwenhoek 2015 Apr;107(4):901–9.
[29] Antonation K, Patel S, Trumble Waddell J, Guillaume Poliquin P, Alexander DC, Hoang L, et al., Canadian Public Health Laboratory Network. Interim laboratory testing guidelines for the detection of non-tuberculous Mycobacterium (NTM) infections in post-operative patients exposed to heater-cooler units. Can Commun Dis Rep 2017 Jan;43(1):25–8.
[30] Alhanna J, Purucker M, Steppert C, Grigull-Daborn A, Schiffel G, Gruber H, et al. Mycobacterium chimaera causes tuberculosis-like infection in a male patient with anorexia nervosa. Int J Eat Disord 2012 Apr;45(3):450–2.
[31] Kasperbauer SH, Daley CL. Mycobacterium chimaera infections related to the heater–cooler unit outbreak: a guide to diagnosis and management. Clin Infect Dis 2018;68(7):1244–50. https://doi.org/10.1093/cid/ciy789. 27.
[32] Moon SM, Kim SY, Jhun BW, Lee H, Park HY, Jeon K, et al. Clinical characteristics and treatment outcomes of pulmonary disease caused by Mycobacterium chimaera. Diagn Microbiol Infect Dis 2016 Dec;86(4):382–4.
[33] van Ingen J, Boeree MJ, van Soolingen D, Mouton JW. Resistance mechanisms and drug susceptibility testing of nontuberculous mycobacteria. Drug Resist Updat 2012 Jun;15(3):149–61.
[34] Perkins KM, Lawsin A, Hasan NA, Strong M, Halpin AL, Rodger RR, et al. Notes from the field: Mycobacterium chimaera contamination of heater-cooler devices used in cardiac surgery - United States. MMWR Morb Mortal Wkly Rep 2016 Oct 14;65(40):1117–8.
[35] Sax H, Bloemberg G, Hasse B, Sommerstein R, Kohler P, Achermann Y, et al. Prolonged outbreak of Mycobacterium chimaera infection after open-chest heart surgery. Clin Infect Dis 2015 Jul 1;61(1):67–75.
[36] Brown-Elliott BA, Nash KA, Wallace RJ. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. Clin Microbiol Rev 2012;25(3):545–82.
[37] CLSI. Susceptibility. Testing of mycobacteria, nocardiae, and other aerobic actinomycetes; approved standard—second edition. CLSI document M24-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
[38] Maurer FP, Pohle P, Kernbach M, Sievert D, Hillemann D, Rupp J, et al. Differential drug susceptibility patterns of Mycobacterium chimaera and other members of the Mycobacterium avium-intracellulare complex. Clin Microbiol Infect 2019 Mar;25(3):379.e1–7.
[39] 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 Nov;72(Suppl 2):ii1–64.
[40] Inderlied CB, Young LS, Yamada JK. Determination of in vitro susceptibility of Mycobacterium avium complex isolates to antimycobacterial agents by various methods. Antimicrob Agents Chemother 1987 Nov;31:1697–702.
[41] Lau D, Cooper R, Chen J, Sim VL, McCombe JA, Tyrrell GJ, et al. Mycobacterium chimaera encephalitis post-cardiac surgery: a new syndrome. Clin Infect Dis 2019 Jun 18. https://doi.org/10.1093/cid/ciz497.

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[42] Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM, Infectious Diseases Society of America Emerging Infections Network. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the emerging infections network. Clin Infect Dis 2008 Jun 1;46(11):1738–40.
[43] van Ingen J, Egelund EF, Levin A, Totten SE, Boeree MJ, Mouton JW, et al. The pharmacokinetics and pharmacodynamics of pulmonary Mycobacterium avium complex disease treatment. Am J Respir Crit Care Med 2012 Sep 15;186(6):559–65.
[44] Sommerstein R, Hasse B, Marschall J, Sax H, Genoni M, Schlegel M, et al., Swiss Chimaera Taskforce. Global health estimate of invasive Mycobacterium chimaera infections associated with heater–cooler devices in cardiac surgery. Emerg Infect Dis 2018;24(3):576–8.
[45] Martin A, Godino IT, Aguilar-Ayala DA, Mathys V, Lounis N, Villalobos HR. In vitro activity of bedaquiline against slow-growing nontuberculous mycobacteria. J Med Microbiol 2019 Aug;68(8):1137–9.
[46] Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. ATS Mycobacterial Diseases Subcommitee; American Thoracic Society, Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.
[47] Riccardi N, Del Puente F, Magnè F, Taramasso L, Di Biagio A. Bedaquiline: a new hope for shorter and better anti-tuberculosis regimens. Recent Pat Anti-Infect Drug Discov 2018;13(1):3–11.
[48] Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern: the Lady Windermere syndrome. Chest 1992 Jun 1;101(6):1605–9.
[49] Esteban J, García-Coca M. Mycobacterium biofilms. Front Microbiol 2018;8:2651. https://doi.org/10.3389/fmicb.2017.02651.
[50] Marra AR, Diekema DJ, Edmond MB. Mycobacterium chimaera infections associated with contaminated heater-cooler devices for cardiac surgery: outbreak management. Clin Infect Dis 2017 Apr 15;65(4):669–74.
[51] United States Food and Drug Administration. Recommendations for the Use of any Heater Cooler Device. Available at: Lastly updated: 19th of December 2018. Accessed: 25th of April 2019, https://www.fda.gov/medicaldevices/productsandmedicalprocedures/cardiovasculardevices/heater-coolerdevices/ucm492583.htm.

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