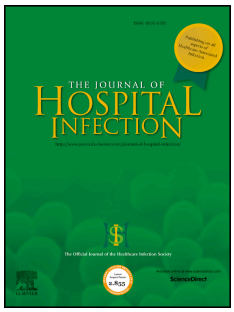
Journal Pre-proof



International Society of Cardiovascular Infectious Diseases Guidelines for the Diagnosis, Treatment and Prevention of Disseminated *Mycobacterium chimaera* Infection Following Cardiac Surgery with Cardiopulmonary Bypass

Barbara Hasse, Margaret Hannan, Peter M. Keller, Florian P. Maurer, Rami Sommerstein, Dominik Mertz, Dirk Wagner, Nuria Fernández-Hidalgo, Jim Nomura, Vinicio Manfrin, Dominique Bettex, Antonio Hernandez Conte, Emanuele Durante-Mangoni, Tommy Hing-Cheung Tang, Rhonda L. Stuart, Jens Lundgren, Steve Gordon, M. Claire Jarashow, Peter W. Schreiber, Stefan Niemann, Thomas A. Kohl, Charles Daley, Andrew J. Stewardson, Cynthia J. Whitener, Kiran Perkins, Diamantis Plachouras, Theresa Lamagni, Meera Chand, Tomas Freiberger, Sandrine Zweifel, Peter Sander, Bettina Schulthess, James Scriven, Hugo Sax, Jakko van Ingen, Carlos A. Mestres, Daniel Diekema, Barbara A. Brown-Elliott, Richard J. Wallace, Jr., Larry M. Baddour, Jose M. Miro, Bruno Hoen, the M. chimaera ISCVID investigators, Infectious Diseases specialists, Hospital epidemiologists, Microbiologists and molecular typing specialists, Cardiac surgeons/ perfusionists/ cardiologists, Ophthalmology, Anaesthesiologists, Public Health

PII: S0195-6701(19)30444-X

DOI: https://doi.org/10.1016/j.jhin.2019.10.009

Reference: YJHIN 5825

To appear in: *Journal of Hospital Infection*

Received Date: 20 September 2019

Accepted Date: 8 October 2019

Please cite this article as: Hasse B, Hannan M, Keller PM, Maurer FP, Sommerstein R, Mertz D, Wagner D, Fernández-Hidalgo N, Nomura J, Manfrin V, Bettex D, Conte AH, Durante-Mangoni E, Hing-Cheung Tang T, Stuart RL, Lundgren J, Gordon S, Jarashow MC, Schreiber PW, Niemann S, Kohl TA, Daley C, Stewardson AJ, Whitener CJ, Perkins K, Plachouras D, Lamagni T, Chand M, Freiberger T, Zweifel S, Sander P, Schulthess B, Scriven J, Sax H, van Ingen J, Mestres CA, Diekema D, Brown-Elliott BA, Wallace Jr RJ, Baddour LM, Miro JM, Hoen B, the M. chimaera ISCVID investigators, Infectious Diseases specialists, Hospital epidemiologists, Microbiologists and molecular typing specialists, Cardiac surgeons/ perfusionists/ cardiologists, Ophthalmology, Anaesthesiologists, Public Health, International Society of Cardiovascular Infectious Diseases Guidelines for the Diagnosis, Treatment and Prevention

of Disseminated *Mycobacterium chimaera* Infection Following Cardiac Surgery with Cardiopulmonary Bypass, *Journal of Hospital Infection*, https://doi.org/10.1016/j.jhin.2019.10.009.

The ISCVID *M. chimaera* investigators

International Society of Cardiovascular Infectious Diseases guidelines for the diagnosis, treatment, and prevention of disseminated *Mycobacterium chimaera* infection following cardiac surgery with cardiopulmonary bypass

The ISCVID *M. chimaera* investigators[*,†]

_____

[*]Corresponding author: B. Hasse. Address: Division of Infectious Diseases and Hospital Epidemiology, University Hospital and University of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. Tel.: +41 44 255 92 37.

[†]Writing group members are listed in the Appendix.

E-mail address: barbara.hasse@usz.ch (B. Hasse).

SUMMARY

Mycobacterial infection-related morbidity and mortality in patients following cardiopulmonary bypass surgery is high and there is a growing need for a consensus-based expert opinion to provide international guidance for diagnosing, preventing, and treating in these patients. In this document the International Society for Cardiovascular Infectious Diseases (ISCVID) covers aspects of prevention (field of hospital epidemiology), clinical management (infectious disease specialists, cardiac surgeons, ophthalmologists, others), laboratory diagnostics (microbiologists, molecular diagnostics), device management (perfusionists, cardiac surgeons), and public health aspects.

Keywords:

Mycobacterial

Cardiopulmonary bypass

Infection

Guidelines

Outbreaks

Heater–cooler device

1. Background

Mycobacterium chimaera is an environmental, slowly growing non-tuberculous mycobacterium (NTM) [1] and, until recently, would have been identified by most clinical microbiology laboratories as *M. intracellulare* or *M. avium* complex (MAC). Prior to this current global outbreak, *M. chimaera* was recognized as a cause of respiratory and disseminated infections among immunocompromised patients [2]. Since 2013, a global outbreak of disseminated *M. chimaera* has been ongoing among patients who underwent open-chest surgery with cardiopulmonary bypass (CPB) [3–25] with all cases linked to

contamination of a specific brand (Stockert 3T; LivaNova, London, UK) of heater–cooler device (HCD) used in CPB [4,26–28]. CPB temporarily replaces cardiopulmonary function during surgery with maintenance of blood flow and oxygenation – thus the common term of 'heart–lung machine' for the CPB pump. HCDs circulate water through heat exchangers and warm or cool blood passing through the CPB and cardioplegia solution circuits. Extracorporeal circulation provides a bloodless field for surgery and maintains vital organ perfusion.

M. chimaera has caused disseminated infections following a variety of open-chest surgeries with CPB, including placement of prosthetic heart valves, prosthetic aortic grafts, and mechanical circulatory support devices [3,7], with a proclivity for ocular involvement [5,15] and granulomatous inflammation in multiple organs in some cases that prompted an initial misdiagnosis of sarcoidosis [3,14,15,29]. Infections following on-pump coronary artery bypass graft (CABG) have also been rarely reported [9,30]. Because there are no international clinical practice guidelines that provide recommendations in the diagnosis, management, and prevention of disseminated *M. chimaera* infections that occur following CPB a multinational collaboration was convened for the development of guidelines that are outlined in this document.

2. Scope and aims

In 2017, the International Society for Cardiovascular Infectious Diseases (ISCVID) recognized the importance of disseminated mycobacterial infections in patients following open-chest surgery with CPB and the growing need for international guidance on diagnosis, management and prevention of these infections. Accordingly, the primary aims of this document were: (i) to provide an update on *M. chimaera* epidemiology and risk factors, (ii) to develop guidelines for diagnosis and management in individual patients, and (iii) to outline infection prevention and control recommendations. This clinical practice guideline was developed by expert consensus after review of available literature. An evidence-based scoring system that was used in the European Society of Cardiology guidelines on infective endocarditis was included in the novel recommendations designated herein (Table Ia,b) [31].

3. Guidelines assembly and conflicts of interest

During the bi-annual ISCVID meeting in Dublin in 2017, an expert consensus group, including infectious diseases specialists, hospital epidemiologists, cardiologists, pathologists, radiologists, and cardiac surgeons, formed a task force to develop recommendations on diagnosis, treatment, and prevention of cardiovascular infections due to *M. chimaera*. Members of this expert group were selected by the ISCVID council to represent a variety of professionals involved in the medical care of patients with cardiovascular infectious diseases.

Moreover, global representatives participated in development of these recommendations. The participants included those with expertise in infection prevention and control, clinical patient management (infectious diseases specialists, cardiac surgeons, ophthalmologists, anaesthesiologists), mycobacteriology laboratory diagnostics (microbiologists with experience in mycobacteriology and molecular diagnostics), device management (perfusionists, infection control specialists), and public health. Participants declared whether they had conflicts of interest which would require disclosure of financial or other interests that could constitute actual, potential, or apparent conflicts. The expert group completed a literature review of studies published since 2013, when the first two cases were published [3]. Medline was searched through the PubMed.gov database using the terms *Mycobacterium chimaera* or *M. chimaera* with the MeSH terms 'treatment', 'cardiac', 'HCD', 'infection control' as well as specific antimicrobials and classes of antimicrobials. Only English language articles were included because the panel members could not reliably review non-English language studies.

4. Epidemiology and risk factors

4.1. Epidemiology and risk factors for HCD-associated M. chimaera infection

The absolute risk of acquiring *M. chimaera* infection is much lower than the risk of other types of infection that complicate open-chest surgeries with CPB including deep sternal surgical site infections (SSIs), hospital-acquired pneumonias or urinary tract infections, and vascular access device infections [8,14]. The estimated risk for *M. chimaera* infection in patients undergoing open-chest surgery necessitating CPB in Switzerland was 11 cases per 14,045 patients with valve procedures, resulting in 0.78 cases per 1000 procedures (95% confidence interval (CI): 0.41–1.45) [32]. In the UK, 16 cases in 112,644 patients with open-chest procedures were initially identified, resulting in 0.14 cases per 1000 procedures (95% CI: 0.08–0.23) [8]. In the USA, numerous hospital-specific prevalence rates range from 1 per 1000 to 1 per 10,000 [26]. Given the long incubation periods and observed change in risk, these estimates are not directly comparable as they are dependent on the years of surgery included and time-point at which the risk estimates were calculated [8].

Reported risk factors for *M. chimaera* infection pertain to the operative procedure (aortic surgery with highest risk) [9], length of exposure to a running HCD [14], specific HCD brand [28], year of manufacture of HCD [33], the applied HCD disinfection measures [34], the distance and positioning of HCD in the operating room (OR) [4,33], and the OR ventilation system [35]. Generation of aerosols from contaminated water systems of operational HCDs may have reached the surgical site through airflow generated by its cooling fans [8]. To date, all clinical cases related to open-chest surgery with CPB have been

associated with the use of Stockert 3T-HCDs (subsequently denoted '3T-HCD') [26–28,30,36,37], which have a market share of about 70%. *M. chimaera* has been cultured in hospital tap water [38] and from water of most types of HCD, and extracorporeal membrane oxygenation (ECMOs) water tanks on the market [39,40]. However, available air sample culture results from HCDs other than 3T have been reported to be negative [28,37]. According to a recent study, air flow direction, location of cooling ventilators, continuous cooling of the water tank at 4°C, and an electronic reminder of disinfection cycle are four relevant differences between the 3T-HCD and Maquet HCU30 and HCU40, which are HCD models, that may contribute to differential infection risk [6]. No published data exist on the respective safety aspects of several other HCD brands and models. Changes in recommended disinfection procedures by LivaNova in September 2014 were not successful in eliminating the risk of *M. chimaera* contamination [41]. Therefore, LivaNova implemented a device modification with installation of an internal sealing and vacuum system on existing 3T-HCD devices in 2017 [42]. Safety data collected following this modification, however, have not been published.

HCDs may be positioned adjacent to the CBP pump, and the exhaust airflow from the HCD may be directed towards the operating field, thus contributing to the risk of *M. chimaera* infection. An OR assessment of 3T-HCD exhaust demonstrated a higher concentration of cumulative particles measured behind the 3T-HCD (near the exhaust fan) than at the surgical field over a 180 min run-time [43]. Using smoke testing, laminar flow ventilation was insufficient to prevent aerosols containing *M. chimaera* generated by the 3T-HCD and circulated by the HCD exhaust fan from dispersing towards the surgical field [35,44].

Interestingly, only one suspected pulmonary *M. chimaera* infection has been reported among exposed OR personnel [45]. Although factors responsible for this observation have not been defined, hypotheses include: (i) *M. chimaera* pulmonary disease will only affect those with pre-existing pulmonary diseases (e.g. bronchiectasis) or with increased susceptibility to mycobacterial disease; (ii) concentration of *M. chimaera* in the air of the OR may not be high enough to cause pulmonary infection, especially in persons without risk factors for developing disease; and (iii) surgical mask use in the OR may provide protection. Identification of other potential respiratory pathogens, including *Legionella* species, in HCD water circuits has previously been recognized as a potential threat to patients and theatre staff [8].

4.2. Population at risk

Based on the evidence to date, the population at risk of disseminated *M. chimaera* infection includes all patients undergoing open-chest surgery with a 3T-HCD running during

surgery, with the implantation of prostheses (e.g. prosthetic valves, vascular grafts, ventricular assist devices) increasing the risk. 3T-HCDs have also been associated with NTM infections other than *M. chimaera* [46]. Patients who underwent a cardiac procedure with 'standby' CPB and therefore a running 'standby' 3T-HCD have an unquantified risk. In contrast to pulmonary NTM disease, where NTM-containing aerosols lead to pulmonary infection in patients with significant underlying structural lung disease (especially in those with underlying bronchiectasis) or who are immunocompromised [47], the transmission route of HCD-related *M. chimaera* infection is non-inhalational and infection can occur in patients without previously known immune deficiency. The likely route of transmission for these non-pulmonary *M. chimaera* infections is direct contamination of the open-chest cavity with *M. chimaera*-containing aerosols during cardiac surgery. Although the majority of infections have followed open-chest cardiac surgery, infections have also been reported among patients following minimally invasive cardiac surgery [21]. The hypothesized route of exposure among the latter is contamination of surgical equipment or grafts in the OR by 3T-HCD-generated bio-aerosols prior to use or implantation during surgery. These infections may involve the heart, due to valve/graft replacements, and may widely disseminate to involve a panoply of body-sites including kidney, liver, bone marrow, bone, vertebra, skin, brain, and choroid. Cardiac conditions at risk of *M. chimaera* infections are listed in Table II.

5. Multidisciplinary hospital patient management

Recommendation

- Management of *M. chimaera*-infected patients by an 'Endocarditis Team' is recommended (Class I, Level C).

The Task Force strongly supports management of *M. chimaera*-infected patients by a multidisciplinary 'Endocarditis Team' [31]. Typically, initial *M. chimaera* infection symptoms are non-specific and often depend on the first body-site or organ involved, the surgical procedure performed, the underlying cardiac disease, and the baseline immunological status of the patient. Hence, the patient may present initially to a variety of medical specialties. Once infection is diagnosed, expertise from various medical specialties is needed including infectious diseases physicians, infection prevention and control practitioners, microbiologists, cardiologists, cardiac surgeons, ophthalmologists, internal medicine specialists, pharmacists, as well as other specialties. Consultation with cardiac imaging specialists is recommended, as echocardiography and nuclear imaging with positron emission tomography/computed tomography are often critical in the diagnosis of infection, determining the extent of dissemination, and follow-up after treatment. Due to the complexity of antibiotic therapy, potential adverse drug effects and drug–drug interactions, antimycobacterial

treatment should be guided by an infectious disease physician in close collaboration with a laboratory microbiologist with expertise in mycobacteriology as well as a clinical pharmacist. Despite the high perioperative risk with resection/excisional surgery, the outcome of patients with disseminated implant-associated infections may be improved when infected prosthetic material is removed [7,9]. Serial discussions with the surgical team and the anaesthesiologist are warranted to determine optimal timing of surgery once a surgical indication is recognized.

6. Diagnosis of *M. chimaera* infection

6.1. Clinical features

The diagnosis of cardiac *M. chimaera* infection can be difficult as initial symptoms may be non-specific, subtle, and appear months to years after surgery [7,8,14,15]. Extrathoracic symptoms may precede cardiac or vascular manifestations [7,10,48] and signs of cardiac infection may be absent and detected only at surgery or post-mortem examination [3,10,49]. Symptom development occurs, on average, 15–17 months post surgery, but the incubation period can range from six weeks to more than five years [9,12,50]. Due, in part, to the long incubation period, clinician suspicion of disseminated *M. chimaera* infection is often low at initial presentation [13]. Non-specific and indolent symptoms often prompt alternative diagnoses [7,14,15]. It is not unusual for affected patients to consult with a variety of specialists before a correct diagnosis is made. Common reported symptoms are prolonged fever, weight loss, generalized malaise and night sweats, with the addition of failure-to-thrive in infants [13]. The physical examination is frequently normal, but in some patients (new onset) heart murmur, signs of embolic complications or hepatosplenomegaly, local signs of sternal SSI, or chorioretinitis are noted.

Cardiovascular diagnoses include prosthetic valve endocarditis [7–10,13,20,21,30], aortic graft infections [7,9,13,15,49], myocarditis [3], infected pseudoaneurysms [22], and cardiovascular implantable electronic device infections [12] or mechanical circulatory support device infections [19]. Infections following on-pump CABG procedures [30] and infections after minimally invasive mitral valve procedures have been rarely reported [21]. Patients with cardiovascular infection due to *M. chimaera* may present with chest pain or signs of sternal SSIs [8,13,14] or mediastinitis [8,16]. Disseminated (extrathoracic) manifestations with bacteraemia may involve a variety of organs, including the lung, spleen, bone marrow, kidney, liver, brain, skin, and bone [3,7,8,10,13–15,20,21,49]. Disseminated *M. chimaera* infections also have a proclivity for ocular [5,15] and central nervous system [7] involvement. Atypical presentations are common [12–14,22,30] and a high index of suspicion is needed to avoid delays in diagnosis. In some cases, a diagnosis of presumptive sarcoidosis has been

made [3,7,13,48] based on granulomatous tissue formation leading to inappropriate immunosuppressive treatment.

Many patients present with evidence of disseminated disease that may include hepatic involvement (elevated transaminases and/or alkaline phosphatase) [18], nephritis (impaired renal function), pneumonitis (impaired diffusion capacity on whole body plethysmography) [3], bone marrow involvement with cytopenia (anaemia, leucocytopenia, and/or thrombocytopenia [7,15]) or haemophagocytic syndrome [12], spine involvement with spondylitis and spondylodiscitis [30], arthritis [7], or splenomegaly. A consistent histopathologic finding upon biopsy of involved body sites is the presence of non-caseating granulomas, often with negative acid-fast bacilli (AFB) smears. Some patients also develop neurological complications with vasculitis of the brain, encephalitis or chorioretinitis [7,15,51].

6.1.1. Chorioretinitis

Chorioretinal lesions may be present in patients presenting with disseminated *M. chimaera* infection [5,15,52]. The patients present with bilateral white-yellowish chorioretinal lesions varying from a few lesions to widespread miliary disease, and a subset of patients have had additional signs of mild anterior uveitis, intermediate uveitis or optic disc swelling [5,52]. Depending on the location of the lesions and the presence of complications such as choroidal neovascularization, these patients might not report visual complaints. Choroidal manifestations in patients with disseminated *M. chimaera* infection are an important clue to this disease. A classification of choroidal lesions based on multi-modal imaging is detailed in Table III, and a recommendation for screening and follow-up ophthalmological examinations in patients with suspected or confirmed *M. chimaera* infection is included in Table IV.

6.1.2. Immune reconstitution inflammatory response syndrome

An immune reconstitution inflammatory syndrome (IRIS) can complicate tuberculosis treatment with a variety of clinical tuberculosis manifestations, with human immunodeficiency virus (HIV) infection being an important risk factor [53]. Nontuberculous mycobacteria usually cause IRIS only in HIV-infected patients [54]. In case of disseminated *M. chimaera* infection, several manifestations occurring after initiation of treatment have represented an IRIS including fever, abscess formations in various body sites (lymph nodes, ovary, spleen, prostate and bone), pancytopenia or chorioretinitis [48]. Patients have typically been treated with corticosteroids (1 mg/kg per body weight) as an adjunct to antimycobacterial therapy. Currently, the long-term outcome and the spectrum of disease of potential *M. chimaera*-related IRIS are yet to be fully defined.

6.2. Imaging techniques

Recommendations

- Transoesophageal echocardiogram for detection of cardiac vegetations, aortic root collections, and evaluation of valvular function is recommended (Class I, Level C).
- ^{18}F-Fluorodeoxy-glucose positron emission tomography (PET)/computed tomography (CT) imaging in case of suspected aortic graft infection or fever of unknown origin (FUO) should be considered (Class IIa, Level C).

In cases of suspected *M. chimaera* infection, echocardiography is central in the diagnosis, surgical assessment and postoperative follow-up [7]. Vegetations, aortic root abscess, valve dysfunction including regurgitation and paravalvular or periprosthetic complications can be identified. Transthoracic echocardiography (TTE) should be performed as part of an initial assessment. However, as most cases have been associated with the presence of prosthetic material, additional transesophageal echocardiography (TOE) is recommended, because of the increased sensitivity of TOE as compared to that of TTE. If extrathoracic infections precede cardiac manifestations, initial echocardiography may be normal [10,15,20,21]. Therefore, repeat TOEs may be needed, especially among patients who do not respond well to antimicrobial treatment. For patients with prosthetic valve endocarditis and aortic graft infections, other imaging techniques such as PET with CT or cardiac contrast-enhanced CT are recommended [15,55,56]. PET/CT, for example, can detect cardiovascular involvement and extracardiac complications when TOE is negative [15,21,56–60], and PET/CT is helpful in treatment monitoring [61].

6.3. Microbiological diagnosis

6.3.1. Laboratory culture methods

Mycobacteria only grow in and on specific media; thus, a high index of suspicion on the side of the clinician is important and correct culture materials (e.g. heparin or sodium citrate blood send for mycobacterial cultures) need to be used. A positive AFB culture for mycobacteria from a specimen taken from a sterile extrapulmonary site (blood, purulent material, bone marrow, tissue, or implanted prosthetic material) should be considered a suspect case. If there is no mycobacterial growth after eight weeks of incubation, the culture is considered negative. Following growth, species identification and antimicrobial susceptibility testing (AST) are necessary to inform treatment. Laboratory culture methods are listed in Table V. For all purulent materials and tissue samples, a combination of solid media (Middlebrook 7H10 or 7H11 or Lowenstein–Jensen) and mycobacterial growth indicator tubes (MGIT; BD, Franklin Lakes, NJ, USA) or other liquid systems such as VersaTrek (Thermo Fisher, Cleveland, OH, USA) should be used to maximize sensitivity [62].

According to a recent case series of 30 patients with *M. chimaera* in the UK, the overall diagnostic sensitivity of one single mycobacterial blood culture is estimated to be 68% with multiple blood or urine cultures increasing the diagnostic yield [9]. An even higher index of suspicion is needed to repeat blood cultures specifically for mycobacteria when initial cultures have not produced growth or if a bacterial PVE is already diagnosed [63].

HCD water samples, if performed, should be cultured as recommended by the ECDC [64]. However, the majority of isolates from HCDs contained mixed populations of two or more strains which led to potential mismatches between environmental and patient cultures in one survey [28].

6.3.2. Molecular diagnosis

Most laboratory methods identify an *M. chimaera* isolate as a member of the *M. avium* complex (MAC) and not all laboratories are able to differentiate *M. chimaera* and *M. intracellulare*. The complete 16S rDNA gene sequences of MAC species differ by only six to 10 base pairs, and only one base pair discriminates *M. chimaera* and *M. intracellulare* [1]. Therefore, sequencing of the 16S–23S internal transcribed spacer region (ITS) has been suggested, albeit rarely available in clinical laboratories [65]. Recent experiences show that sequencing of the first 500 bp of the 16S rRNA gene (rrs) is sufficient to discriminate *M. chimaera* and *M. intracellulare* (included in MicroSeq; Applied Biosystems, Thermo Fisher, Foster City, CA, USA).

Another method is hsp65 sequencing [1]. Researchers have developed a novel reverse hybridization of PCR product-based assay (GenoType NTM-DR ver. 1.0; Hain Lifescience, Nehren, Germany) with 100% specificity for identifying *M. chimaera* in 173 isolates [66,67]. Because the differentiation of MAC species is challenging and expensive in a diagnostic setting, Bruker has recently developed an improved algorithm to differentiate pathogenic species based on differential spectral peak signatures, by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on a commercially available platform. The results are promising with identification of 100% of the *M. intracellulare* and 82% of the *M. chimaera* isolates [68].

A TaqMan quantitative polymerase chain reaction (qPCR) assay has been developed to facilitate a rapid diagnosis of *M. chimaera* infection [69]. With this method, *M. chimaera* could be detected *ex vivo* at low concentrations (with a limit of 100 cfu/mL in whole blood) in human blood samples [69]. Of note, blood anticoagulated with sodium citrate or EDTA and not heparin should be used for PCR testing.

6.3.3. Whole genome sequencing

For genotyping, whole genome sequencing of clinical and HCD isolates should be the preferred method to confirm relatedness to the HCD outbreak strain [8,26–28,37,70]. Phylogenetic signature single nucleotide polymorphisms (SNPs) can also be used to identify certain groups/clades of *M. chimaera*, including the outbreak clade [28]. Karius (Redwood City, CA, USA) developed a next-generation sequencing test specifically to detect *M. chimaera* in plasma samples [71,72].

Remarkably, whole genome sequencing results have supported a common source of the current global *M. chimaera* outbreak. Most studies revealed that the majority of patient isolates, HCD water and air isolates from multiple countries were very closely related with differences of single nucleotide polymorphisms of fewer than 10 variants [8,26–28,37,70]. One large European sequencing study [28] included 250 isolates of *M. chimaera* and all but one isolate from a patient with prior open-heart surgeries clustered in the outbreak group 1.1 (median of only four SNP differences among them). This group also included HCD water and air isolates and one isolate from the LivaNova factory and a Maquet ECMO device. However, there were several HCD isolates not clustering in group 1.1. Additionally, two studies revealed that *M. chimaera* could be detected in factory-new assembled HCDs and from the pump assembly area [28,30] implicating contamination with *M. chimaera* at the LivaNova factory as the most likely source of the worldwide outbreak. Most researchers are concerned that all HCD made by this manufacturer over the past decade may have been contaminated with the *M. chimaera* outbreak strain [37].

6.3.4. Microbiological diagnostic algorithm for suspected M. chimaera infection

Recommendations

- Among patients with prosthetic valves/rings, aortic grafts and mechanical circulatory devices, conventional blood cultures off antibiotics are recommended for any undefined febrile illness for which antimicrobials are being considered (Class I, Level C).
- If the above are negative and cardiovascular infection is still in the differential based on when the patient was exposed to 3T-HCD, multiple mycobacterial (heparin or sodium citrate) blood cultures are recommended (Class I, Level C). Consider also specific mycobacterium genus-specific PCR from whole blood (Class IIa, Level C).
- AFB stain and culture of cardiac or other affected tissue (sputum, urine, kidney, liver, skin) are recommended (Class I, Level C). Consider also species-specific PCR or mycobacterium genus-specific PCR followed by next-generation sequencing from plasma (Class IIa, Level C).

- If cytopenias are present, bone marrow biopsy should be considered for histology, staining and mycobacterial culture (Class IIa, Level C).
- In case of FUO, if initial mycobacterial blood cultures are unrevealing, repeat mycobacterial blood cultures and mycobacterium genus-specific PCR from whole blood or NGS from plasma should be considered (Class IIa, Level C).

Early detection of cardiovascular infection (regardless of pathogen) is important. In most instances the pathogen will not be *M. chimaera*. Therefore, blood cultures off antibiotics are important, and physicians need to routinely encourage all patients with cardiac valves, repairs, or history of infective endocarditis to request blood cultures before being placed on empiric antimicrobials for a febrile illness [73].

The crucial point in patients with suspected *M. chimaera* infection is a prior history of surgery requiring CPB (exposure criterion). When conventional blood cultures are negative and infective endocarditis or aortic graft infection is suspected, serological testing as suggested for culture-negative endocarditis should be done [31]. Bacterial blood cultures (i.e. non-mycobacterial) should be incubated for at least seven to 10 days, whereas mycobacterial blood cultures should be incubated for at least 56 days. In cases involving redo cardiac surgery, tissue cultures (for both bacteria as well as mycobacteria), broad-range and mycobacterium genus-specific PCR (covering NTM) as well as histopathology should be performed. A laboratory diagnostic algorithm in case of suspected *M. chimaera* infection is provided in Figure 1.

6.4. Histopathological diagnosis of M. chimaera infection

Recommendations

- Resected cardiac valve or other infected tissue and embolic fragments should be examined for possible mycobacterial infection (Class I, Level C).
- Mycobacterium genus-specific PCR should be considered if histopathology shows non-caseating granulomas and foamy swollen macrophages with/without acid-fast bacilli (Class IIa, Level C).

The histopathological standard to confirm a diagnosis of infective endocarditis in patients undergoing surgery for proven or suspected endocarditis is the presence of inflammation, neovascularization, and organisms. AFB stains from unfixed valve tissue should be done in all cases if a pathogen is not identified by conventional bacteriological methods. The detection of non-caseating granulomas and foamy swollen macrophages with/without AFB is consistent with NTM infection, including those by *M. chimaera* in the appropriate clinical setting [3,5,7]. Granulomatous lesions have also been described in the liver, kidney, lung, choroid, bone, myocardium, bone marrow, skin, and muscles among

patients with disseminated *M. chimaera* infection [3,7,18]. Resected cardiac valve or other infected tissue and embolic fragments should be examined for suspected mycobacterial infection. Additionally, the tissue sample should be sent to a microbiology laboratory for identification of micro-organisms and performance of mycobacterium genus-specific PCR [74]. Because the sensitivity of PCRs performed on paraffin-embedded specimens is generally lower as compared to that of natural specimens [3,75], a short-amplicon PCR targeting the mycobacterial *hsp65* gene may be considered [76].

6.5. Diagnostic criteria

Diagnostic criteria for *M. chimaera* infection are presented in Table V. The long latency and the protean clinical presentation complicate securing an early diagnosis. Thus, the criteria used in the 2015 European Society of Cardiology guidelines for the diagnosis of IE are not applicable in these patients[31]. Moreover, sporadic cases with bacteraemia and disseminated infections without obvious signs of valve involvement have occurred [3,49].

7. Antimicrobial therapy

7.1. Antimicrobial therapy

Recommendations

- Use of combination therapy with azithromycin (or clarithromycin) with ethambutol, and a rifamycin (Class I, Level C), whereby the macrolide is the cornerstone of therapy, thus should *not* be given as a monotherapy at any time (Class III, Level C).
- Amikacin is recommended and continued for as long as tolerated via peripherally inserted central catheter as outpatient parenteral antibiotic therapy (Class IIa, Level C).

Table VI lists regimens for *M. chimaera* treatment. Currently, we are unable to provide a definitive recommendation regarding the duration of treatment. However, some investigators have followed with monthly mycobacterial blood cultures and treatment for a minimum of 12 months after conversion of blood cultures or redo surgery. For patients who are not candidates for additional cardiovascular surgery, long-term suppressive antibiotic therapy such as used in disseminated MAC infection might be considered.

Combination therapy consisting of azithromycin (or clarithromycin) with ethambutol, and a rifamycin, is recommended for treatment of disseminated MAC infections among people living with HIV infection [47]. A macrolide is considered the cornerstone of therapy for MAC infections [47], whereas the combination with a rifamycin is to prevent macrolide resistance selection. Drug–drug interaction due to azithromycin and rifamycin is less [77] and the azithromycin tolerability is in general better than for clarithromycin, thus azithromycin is preferred over clarithromycin. We strongly discourage one- or two-drug therapy (especially

macrolide monotherapy) due to subsequent rapid development of macrolide resistance due to a 23S rRNA gene mutation [47,78,79] and of amikacin resistance due to a 16S rRNA gene mutation [79]. This resistance has been observed in disseminated disease due to HIV and in pulmonary disease treated with these agents.

During the initial (and perioperative) phase, intravenous amikacin is recommended for six to 12 weeks to increase the speed of sterilization of blood cultures and valves/abscesses, and subsequently amikacin treatment should be continued as long as tolerated. Due to the severity of *M. chimaera* infection, many clinicians added a fifth antimicrobial agent to the regimen, such as clofazimine, which *in vitro* has shown synergistic effects with amikacin [80]. Moxifloxacin [81] or linezolid are alternatives; however, since the modal MICs of moxifloxacin and linezolid are high this is of questionable benefit [82]. There are limited in-vitro data regarding antibacterial activity of bedaquiline against MAC [62,83–85], although off-label use for *M. chimaera* treatment has been reported in several countries.

7.2. Adverse drug reactions of antimicrobial agents and therapeutic drug monitoring

Recommendations

- Monitoring of vestibular function and audiograms is recommended (monthly in patients receiving amikacin; every second month in patients receiving macrolides) (Class I, Level C).
- Periodic ophthalmologic examinations with visual acuity, red–green colour discrimination, confrontation visual field testing, and dilated fundus examination is recommended in patients receiving ethambutol, linezolid, and/or rifabutin (Class I, Level C).
- Monthly electrocardiograms are recommended in patients receiving macrolides, quinolones, clofazimine, linezolid, and bedaquiline (Class I, Level C).
- Weekly therapeutic drug monitoring (TDM) is recommended in patients receiving amikacin. In patients with renal insufficiency receiving ethambutol, TDM is recommended at baseline and until steady state of therapeutic levels (Class I, Level C).
- Monitoring of macrolide blood levels may be considered especially when rifampin is combined with clarithromycin (Class IIb, Level C).

Many patients with disseminated *M. chimaera* infection experience adverse drug reactions [7] due to innate toxicity. Antimycobacterial antibiotics with *M. chimaera* activity and their more common adverse drug reactions are listed in Table VII. Auditory and vestibular function may be impaired by amikacin, clarithromycin, and azithromycin, and vestibular function screening and audiograms should be monitored. In addition, renal function

should be monitored at least once weekly in patients who receive amikacin. Due to increased ocular toxicity of ethambutol, rifabutin, and linezolid [86], baseline and then periodic ophthalmologic examinations with visual acuity (ethambutol/rifabutin), red–green colour discrimination (ethambutol), and dilated fundus examination are recommended. This is needed if they have infection-related and/or IRIS-related ocular involvement [52]. Due to the risk of QTc-interval prolongation (associated with macrolide/rifabutin/bedaquiline/moxifloxacin and linezolid treatment) monthly electrocardiograms are recommended.

Therapeutic drug monitoring (TDM) is always recommended in patients receiving amikacin treatment, and more closely in patients with impaired renal function. Clarithromycin enhances rifabutin toxicity (especially uveitis), whereas rifampicin lowers clarithromycin serum drug levels [77,87]. However, this has not been shown to impact clinical outcome. Since low macrolide drug concentrations due to drug–drug interactions have been described [88], monitoring for azithromycin or clarithromycin blood levels should be considered among all patients with *M. chimaera* infection [89].

7.3. Susceptibility to antimicrobial agents

Recommendations

- Antimicrobial susceptibility testing of *M. chimaera* isolates should be performed by experienced reference laboratories (Class I, Level C).
- *M. chimaera* isolates should be saved for future testing if no baseline AST has been performed (Class I, Level C).
- Clarithromycin and amikacin MIC testing is recommended (Class I, Level C).

Criteria for AST of NTM were established by the Clinical and Laboratory Standards Institute (CLSI) in November 2018. Breakpoints for antimicrobials used in the treatment of NTM infections were re-defined in the M24Ed3 and M62Ed1 CLSI documents, respectively [90,91]. To ensure optimal results, AST of *M. chimaera* isolates should be performed by experienced reference laboratories [92]. Baseline macrolide AST should be performed for clarithromycin, as the solubility at high concentrations is increased as compared to that of azithromycin [79,93,94]. Furthermore AST is recommended for (i) blood culture isolates from patients receiving macrolides, (ii) clinically significant isolates of patients who received macrolide treatment, and (iii) isolates recovered from patients with relapsing infection following completion of a macrolide-containing regimen. As in other clinically relevant NTM infections, *M. chimaera* isolates should be saved for future testing if no baseline AST has been performed [79,93,94].

The minimum inhibitory concentration (MIC) of antimicrobials to which an organism's growth is inhibited (in µg/mL, indexed to base 1) should be determined in slowly growing mycobacteria by broth microdilution in Mueller–Hinton broth [93,94]. All baseline *M. chimaera* clinical isolates regardless of source have very similar MICs to any drug. It remains unclear if the fact that post-CPB surgery infections have a common source of infection contributes to the particular AST pattern. Wild-type *M. chimaera* strains are susceptible to macrolides [7,15,95] and, to date, no isolate with clarithromycin resistance has been recovered [7,15,82]. One patient who received prolonged macrolide treatment and suffered infection relapse had an isolate that demonstrated intermediate resistance to clarithromycin (MIC of ≥16 to ≥32 µg/mL depending on pH) [52].

Routine susceptibility testing of antimycobacterial agents other than clarithromycin is not recommended [79], since reported AST of rifampin, rifabutin, ethambutol and streptomycin do not predict therapeutic efficacy. However, we recommend primary testing of amikacin against MAC isolates, extrapolating breakpoints from rapidly growing mycobacteria (susceptible: ≤16 mg/L; intermediate: 32 mg/L; resistant: ≥64 mg/L) [91,96], since amikacin is a key component of regimens to treat complicated MAC infections and since it has often been used in the pre- and postoperative phase of *M. chimaera* infection [7,15,82].

8. Surgical intervention

8.1. Pre- and perioperative management

Recommendations on the perioperative management and the hospital epidemiology precautions for patients who require repeat surgery in the treatment of cardiovascular infection due to *M. chimaera* are summarized in Table VIII. Coronary angiography and intraoperative echocardiography should be performed as recommended by the ESC guidelines [31]. Recommendations for SSI prophylaxis for cardiac procedures should be followed [97]. In addition, *M. chimaera* treatment should be continued in the perioperative phase. Isolation precautions in the pre- and post-anaesthesia care unit are not required.

8.2. Surgical approach

Recommendation

- Revision surgery with removal of all cardiovascular prosthetic material should be considered (Class IIa, Level C). Source control should include all extracardiac foci in addition to cardiovascular sites (Class IIa, Level C).

Cardiovascular *M. chimaera* infection is associated with a high morbidity and mortality due, in part, to both dissemination of infection and high affinity of mycobacteria to attach to, and form biofilm on, the surface of cardiovascular prosthetic devices. Many patients managed conservatively with antimycobacterial treatment alone have either failed to improve

or have experienced breakthrough infection [3,7]. Hence, redo surgery with removal of all cardiovascular prosthetic material should be considered. Intraoperative mycobacterial tissue cultures and mycobacterium genus-specific PCR followed by sequencing must be obtained because culture results have been positive in the bulk of patients, regardless of whether or not anti-mycobacterial therapy has been previously administered [9]. Removal of all intracardiac foreign material is strongly recommended due to mycobacterial biofilm formation, even if a cardiac valve/vascular graft is functioning well. Additionally, extraction and replacement of any other cardiovascular prosthetic devices is recommended. Patients with localized (e.g. sternal surgical site) infections should undergo extensive debridement with removal of sternal metal wires [3,7,9,49]. Nevertheless, there are patients in whom extensive surgical intervention is not feasible, usually due to a patient's underlying co-morbid conditions, and an individualized approach to infection management is needed. The optimal timing of a redo cardiovascular surgical procedure remains undefined. If feasible, it may be prudent to wait for clearance of mycobacterial blood cultures. Several centres advise preoperative anti-mycobacterial therapy for 6–12 weeks to reduce the chance of planktonic forms seeding replacement devices [7,49]. Whether antimycobacterial therapy prior to surgery and removal of all prosthetic material influences infection cure rates remains to be defined by longer follow-up periods with a larger number of patients [7,9,13,48].

There is no preference for a specific valve/graft substitute as there are insufficient data to make a recommendation. The use of cryopreserved homografts should be considered in the setting of aortic graft infections and annular abscess formation. However, availability of human tissue for transplantation is an important consideration as not all institutions have access, especially in urgent cases. Heart transplantation is considered in extreme infective endocarditis cases where operative procedures fail, provided repeated blood cultures are negative. Due to the need for immunosuppression, heart transplantation for disseminated *M. chimaera* infection generally has not been considered a feasible option. Extrathoracic and disseminated *M. chimaera* infections are common. Ideally, non-cardiovascular foci (e.g. bone infections and abscesses) should be eradicated before cardiovascular surgical intervention [22]. If cardiac surgery cannot be delayed, distant infection sites should be eradicated before the end of antimycobacterial therapy. In some cases, surgical intervention at non-cardiovascular infection sites will also be required.

9. Follow-up and prognosis

Relapse is a major complication of disseminated *M. chimaera* infection that often requires repetitive surgery involving cardiovascular and/or non-cardiovascular sites [7,9,13]. Factors associated with relapse are included in Table IX. Currently, the actual infection

relapse risk is undefined, in part related to the extended follow-up that is required after completion of antimycobacterial therapy to determine whether cure of infection has been achieved. Among the few reported survivors with defined follow-up, the relapse rate has been as high as 30–50% [7,9]. However, the retrospective nature of most case series with broad-ranging follow-up periods and the prolonged incubation period of infection due to *M. chimaera* make quantitating outcome analyses difficult. Elevated mortality is another troubling outcome, with recent case series reporting mortality rates of 20–67% [7,9,13,14,21,30].

10. Considerations for patient notification, screening, and investigation

Recommendations

- Consider patient and provider notification regarding risk and signs/symptoms of infection (Class IIa, Level C).
- Additional case-finding through investigation and testing of patients with a history of exposure to 3T-HCD should be restricted to those who are symptomatic (Table X) (Class IIa, Level C).

Patients who have undergone CPB should be educated about the risks, until they reach the fifth-year anniversary of their surgery, so that patients can seek medical care if warning signs and symptoms of *M. chimaera* infection develop. Given the higher yield among hospitals that have already had a case (in addition to the medico-legal component), this recommendation applies in particular to sites with at least one case.

Providers who see exposed patients, such as primary care providers, should be notified to increase awareness of the risks associated with exposure to CPB. Provider awareness can be achieved through public health alerts, webinars, or by e-mails to various healthcare-provider professional societies. Additionally, the use of ‘alerts’ embedded in electronic medical records of patients who underwent open-chest surgery and who may be at risk of future *M. chimaera* infection may allow providers to more rapidly diagnose and refer patients for infectious disease consultation.

Investigators in the USA have implemented both patient and healthcare provider notifications to help identify potentially infected patients early [98,99]. In 2016, CDC issued a recommendation that all US healthcare facilities using the 3T-HCD notify patients who underwent open-chest cardiac surgery using these devices of the risk of *M. chimaera* infection. Patient notification letters provided information on the signs and symptoms of a possible infection and patients were encouraged to promptly seek medical care if experiencing any of these symptoms [99]. To date, a number of infected patients and clusters have been identified through this strategy, including one institution with a large outbreak that was not

previously recognized [18,98]. Additionally, consideration should be given to patients who will be undergoing cardiac surgery with a 3T-HCD to notify them of the potential risks of *M. chimaera* infection through a preoperative informed consent process [100].

The task force recommends that additional case-finding through evaluation and testing be restricted to patients previously exposed to HCD who develop symptoms (Table X), given the low disease incidence, the significant psychological impact and the overall costs of screening. Additional cases of *M. chimaera* infections might be found by review of: (i) non-respiratory *M. avium* complex isolates with former CPB with the use of 3T-HCD within five to six years; (ii) histopathology reports of culture-negative cardiovascular infections with former CPB with the use of 3T-HCD within five to six years; (iii) sarcoidosis cases and former CPB with the use of 3T-HCD within five to six years.

Recommendations regarding systematic screening for *M. chimaera* infection among asymptomatic patients with a prior history of open-chest surgery have been considered by several health agencies, with the assumption that this might result in an earlier diagnosis and a reduction in dissemination of infection. However, the time between index surgery and diagnosis of infection has been broad and ranged between six weeks to more than five years (median: 15 months) [9,12]; thus screening, if performed, would have to be done on a recurrent basis. Moreover, screening tools, such as routine and/or mycobacterial blood cultures, have a low sensitivity for detecting *M. chimaera* [7]. In addition, it is not clear which screening tests might provide the greatest yield.

11. Prevention, infection control measures and reporting obligation

Co-ordination and surveillance of risk mitigation measures (Table XI) should be the responsibility of each institution's infection prevention and control experts, who are familiar with the biology of *M. chimaera* and its proclivity to cause device contamination in certain settings. Institutions should also refer to relevant guidance from regional regulatory and public health providers. In particular, the preferential adherence of mycobacteria to surfaces at air–water interfaces and the high cell-surface hydrophobicity contribute to the disinfection tolerance of mycobacteria [34,41,103–106]. Additionally, NTM can grow over a very wide temperature range (15–45°C) and survive at 55–60°C [65]. Since decontamination measures often fail [41,91,92] and since intensified cleaning and disinfection might lead to device damage [36,106], facilities can either use other HCDs or they are strongly advised to separate HCDs from the OR room air volume by: (i) placing HCDs in dedicated utility rooms adjacent to the OR [33,102,107,108]; or (ii) encasing them with controlled air extraction via a duct to the theatre exhaust conduit [41]. However, encasings that are engineered and built by hospitals may alter the function of the HCD, and the potential for such changes in function

should be taken into consideration when implementing such interventions. Removal of HCDs from the OR may require reconfiguration of ORs and the theatre design may prevent removal of the implicated HCDs [108]. If HCD exhaust air cannot be reliably separated from the OR, HCDs should be placed as far as possible away from the operating field and the vent exhaust should be directed away from the patient and the surgical instruments [107,108,109]. These measures should be considered only temporary, as the risk of airborne transmission is not eliminated. Additionally, cross-contamination by exchanging tubing from one HCD to another should be avoided [33,110].

Institutions should continue to follow updated manufacturer instructions for cleaning and disinfection of these devices [110]. More recently, LivaNova issued updated instructions in the monitoring of hydrogen peroxide concentrations in the HCD water circuit [110]. The manufacturer also implemented device modifications consisting of a vacuum and sealing upgrade and an aerosol collection kit in 2017 [42]. Currently, we cannot make a statement with regard to the safety of these modifications due to a lack of data. Additionally, LivaNova offers a refurbishing and disinfection programme of their 3T-HCD with replacement of accessories, tubing and connectors to prevent recontamination [34]. However, there is no consistent evidence that *M. chimaera* can be eradicated from any HCD model once contaminated.

Some advocate routine microbiological screening of HCDs. However, there is no standardization with regard to the collection of samples and the laboratory methods used, with differences among environmental laboratories. In addition, the degree of device contamination required to generate positive HCD water and air cultures is unknown, thus the ultimate benefit is uncertain. Water samples of 1000 mL cultured in Mycobacteria Growth Indicator Tubes (MGIT^{TM}) medium had the highest sensitivity for *M. chimaera* detection in a recent study [112]. Routine surveillance is not widely adopted due to slow growth of this organism in laboratory cultures, which can take up to eight weeks; this delay may lead to the use of contaminated machines during this prolonged incubation period [108,112]. Additionally, sampling and testing protocols have not been validated, with some concern for false-negative results.

Reporting of adverse events that occur as a result of medical device use is encouraged in most jurisdictions. Healthcare professionals should report cases of *M. chimaera* infection thought to be associated with use of a contaminated HCD to the respective regulatory authority [101].

12. Areas of future research

As highlighted throughout this document, there are many aspects of diagnosis, management, and prevention that need further research. The results of subsequent investigations will not only be critical with regard to improved understanding of post-cardiovascular surgical *M. chimaera* infections, but will also help to gain insight into other types of mycobacterial infections acquired in the operative setting [113].

The extent of this outbreak and especially the risk to the paediatric population are undefined [7,114]. Case-finding strategies, device safety alerts, and microbiological diagnostics need improvements [107]. Due to the rarity of the disease, the task force strongly encourages multi-centre outcomes data collections to address key questions regarding optimal medical therapy, which is currently undefined. There are currently efforts to create a US registry of patients infected with NTM after exposure to HCDs during cardiac surgery, and the registry hopes to provide more details and guidance on the epidemiology, clinical manifestations, treatment, and outcomes for patients with related infections. Additional details regarding enrolling patients to the registry can be found at http://www.NTMInfect.org. The correlation between treatment response and in-vitro susceptibility of the isolates to anti-mycobacterial drugs needs further study. The role of therapeutic drug monitoring also requires clarification [7]. Collaborative discussions between medical device manufacturers, engineers, and hospital epidemiology experts will be needed as new HCDs are designed. Additionally, reliable decontamination and identification of agents that can disrupt biofilms and increase chlorine susceptibility of mycobacteria are required [115]. Moreover, other mycobacteria [46,101,116] as well as fungi, *Legionella* spp., non-fermenters such as *Pseudomonas aeruginosa*, coagulase-negative staphylococci, *Micrococcus* spp. and Gram-positive rods may also colonize HCDs [104] although the clinical relevance of colonization of HCDs with one or more of these organisms is unclear [46,116].

Conflict of interest statement

None declared.

Funding sources

There was no external funding source. B.H.'s work was supported by the Swiss National Science Foundation, grant number 32473B_163132/1; J.M.M. received a personal 80:20 research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017 to 2019.

Appendix

ISCVID writing group members are listed at: …

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] Schweickert B, Goldenberg O, Richter E, Gobel UB, Petrich A, Buchholz P, et al. Occurrence and clinical relevance of *Mycobacterium chimaera* sp. nov., Germany. Emerg Infect Dis 2008;14:1443–6.

[3] 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.

[4] 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;61:67–75.

[5] Zweifel SA, Mihic-Probst D, Curcio CA, Barthelmes D, Thielken A, Keller PM, et al. Clinical and histopathologic ocular findings in disseminated *Mycobacterium chimaera* infection after cardiothoracic surgery. Ophthalmology 2017;124:178–88.

[6] Kuehl R, Banderet F, Egli A, Keller PM, Frei R, Dobele T, et al. Different types of heater–cooler units and their risk of transmission of *Mycobacterium chimaera* during open-heart surgery: clues from device design. Infect Control Hosp Epidemiol 2018;39:834–40.

[7] 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;36:2745–53.

[8] Chand M, Lamagni T, Kranzer K, Hedge J, Moore G, Parks S, et al. Insidious risk of severe *Mycobacterium chimaera* infection in cardiac surgery patients. Clin Infect Dis 2017;64:335–42.

[9] 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;24:1164–70.

[10] Chiesi S, Piacentini D, Salerno ND, Luise D, Peracchi M, Concia E, et al. Disseminated *Mycobacterium chimaera* infection after open heart surgery in an Italian woman: a case report and a review of the literature. Infez Med 2017;25:267–9.

[11] Cappabianca G, Paparella D, D'Onofrio A, Caprili L, Minniti G, Lanzafame M, et al. *Mycobacterium chimaera* infections following cardiac surgery in Italy: results from a National Survey Endorsed by the Italian Society of Cardiac Surgery. J Cardiovasc Med (Hagerstown) 2018;19:748–55.

[12] Gasch O, Meije Y, Espasa M, Font B, Jimenez S, Fernandez-Hidalgo N. Disseminated infection due to *Mycobacterium chimaera* after aortic valve replacement. Rev Esp Cardiol (Engl Ed) 2019;72:502–3.

[13] Appenheimer A. *Mycobacterium chimaera* outbreak response: experience from four US healthcare systems (Abstrct 2391). ID Week 2016, New Orleans, LA, October 29th, 2016. Available at: hhhtx/idsaconfexcom/idsa/2016/webprogram/Paper 60925 [last accessed April 2017].

[14] Lyman MM, Grigg C, Kinsey CB, Keckler MS, Moulton-Meissner H, Cooper E, et al. Invasive nontuberculous mycobacterial infections among cardiothoracic surgical patients exposed to heater–cooler devices. Emerg Infect Dis 2017;23:796–805.

[15] Tan N, Sampath R, Abu Saleh OM, Tweet MS, Jevremovic D, Alniemi S, et al. Disseminated *Mycobacterium chimaera* infection after cardiothoracic surgery. Open Forum Infect Dis 2016;3:ofw131.

[16] Oda G, Ryono R, Lucero-Obusan C, Schirmer P, Shanawani H, Jacobs K, et al. Epidemiologic review of veterans health administration patients with isolation of nontuberculous mycobacteria after cardiopulmonary bypass procedures. Infect Control Hosp Epidemiol 2017;38:1103–6.

[17] Rudikoff AG, Ganocy TK, Kansagra K, Torres FA, Humphries BD, Hernandez Conte A. Thoracolumbar osteomyelitis secondary to systemic *Mycobacterium chimaera* infection status post aortic valve replacement. J Cardiothoracic Vasc Anesth 2019;33:1704–9.

[18] Shafizadeh N, Hale G, Bhatnagar J, Alshak NS, Nomura J. *Mycobacterium chimaera* hepatitis: a new disease entity. Am J Surg Pathol 2019;43:244–50.

[19] Balsam LB, Louie E, Hill F, Levine J, Phillips MS. *Mycobacterium chimaera* left ventricular assist device infections. J Card Surg 2017;32:402–4.

[20] Cai Y, Landolfo K, Renew JR. Mycobacterium infection from a cardiopulmonary bypass heater–cooler unit in a patient with steroid-induced immunosuppression. Can J Anaesth 2017;64:513–16.

[21] Hamad R, Noly PE, Perrault LP, Pellerin M, Demers P. *Mycobacterium chimaera* infection after cardiac surgery: first Canadian outbreak. Ann Thorac Surg 2017;104:e43–e5.

[22] O'Neil CR, Taylor G, Smith S, Joffe AM, Antonation K, Shafran S, et al. *Mycobacterium chimaera* infection after aortic valve replacement presenting with aortic dissection and pseudoaneurysm. Open Forum Infect Dis 2018;5:ofy018.

[23] Stewardson AJ, Stuart RL, Cheng AC, Johnson PD. *Mycobacterium chimaera* and cardiac surgery. Med J Aust 2017;206:132–5.

[24] Overton K, Mennon V, Mothobi N, Neild B, Martinez E, Masters J, et al. Cluster of invasive *Mycobacteria chimaera* infections following cardiac surgery demonstrating novel clinical features and risks of aortic valve replacement. Intern Med J 2018;48:1514–20.

[25] Zhang X, Lin J, Feng Y, Wang X, McNally A, Zong Z. Identification of *Mycobacterium chimaera* in heater–cooler units in China. Sci Rep 2018;8:7843.

[26] 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. Morb Mortal Wkly Rep 2016;65:1117–18.

[27] Williamson D, Howden B, Stinear T. *Mycobacterium chimaera* spread from heating and cooling units in heart surgery. New Engl J Med 2017;376:600–2.

[28] van Ingen J, Kohl TA, Kranzer K, Hasse B, Keller PM, Katarzyna Szafranska A, et al. Global outbreak of severe *Mycobacterium chimaera* disease after cardiac surgery: a molecular epidemiological study. Lancet Infect Dis 2017;17:1033–41.

[29] Ganatra S, Sharma A, D'Agostino R, Gage T, Kinnunen P. *Mycobacterium chimaera* mimicking sarcoidosis. Methodist Debakey Cardiovasc J 2018;14:301–2.

[30] Haller S, Holler C, Jacobshagen A, Hamouda O, Abu Sin M, Monnet DL, et al. Contamination during production of heater–cooler units by *Mycobacterium chimaera* potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016. Euro Surveill 2016;21.

[31] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075–128.

[32] Sommerstein R, Hasse B, Marschall J, Sax H, Genoni M, Schlegel M, et al. Global health estimate of invasive *Mycobacterium chimaera* infections associated with heater–cooler devices in cardiac surgery. Emerg Infect Dis 2018;24:576–8.

[33] Sommerstein R, Schreiber PW, Diekema DJ, Edmond MB, Hasse B, Marschall J, et al. *Mycobacterium chimaera* outbreak associated with heater–cooler devices: piecing the puzzle together. Infect Control Hosp Epidemiol 2017;38:103–8.

[34] Garvey MI, Ashford R, Bradley CW, Bradley CR, Martin TA, Walker J, et al. Decontamination of heater–cooler units associated with contamination by atypical mycobacteria. J Hosp Infect 2016;93:229–34.

[35] Sommerstein R, Ruegg C, Kohler P, Bloemberg G, Kuster SP, Sax H Transmission of *Mycobacterium chimaera* from heater–cooler units during cardiac surgery despite an ultraclean air ventilation system. Emerg Infect Dis 2016;22:1008–13.

[36] Centers for Disease Control and Prevention. Non-tuberculous mycobacterium (NTM) infections and heater–cooler devices interim practical guidance. Atlanta: CDC; October 2015. Available at: http://www.cdc.gov/HAI/pdfs/outbreaks/CDC-Notice-Heater-Cooler-Units-final-clean.pdf [last accessed March 2016].

[37] Svensson E, Jensen ET, Rasmussen EM, Folkvardsen DB, Norman A, Lillebaek T. *Mycobacterium chimaera* in heater–cooler units in denmark related to isolates from the United States and United Kingdom. Emerg Infect Dis 2017;23.

[38] Lande L, Alexander DC, Wallace RJ, Jr, Kwait R, Iakhiaeva E, Williams M, et al. *Mycobacterium avium* in community and household water, suburban Philadelphia, Pennsylvania, USA, 2010–2012. Emerg Infect Dis 2019;25:473–81.

[39] Kuehl R, Banderet F, Egli A, Keller PM, Frei R, Dobele T, et al. Different types of heater–cooler units and their risk of transmission of *Mycobacterium chimaera* during open-heart surgery: clues from device design. Infect Control Hosp Epidemiol 2018;39:834–40.

[40] Trudzinski FC, Schlotthauer U, Kamp A, Hennemann K, Muellenbach RM, Reischl U, et al. Clinical implications of *Mycobacterium chimaera* detection in thermoregulatory devices used for extracorporeal membrane oxygenation (ECMO), Germany, 2015 to 2016. Euro Surveill 2016;21.

[41] Schreiber PW, Kuster SP, Hasse B, Bayard C, Ruegg C, Kohler P, et al. Reemergence of *Mycobacterium chimaera* in heater–cooler units despite intensified cleaning and disinfection protocol. Emerg Infect Dis 2016;22:1830–3.

[42] LivaNova implements 3T heater–cooler device modification. 2018. Available at: https://investor.livanova.com/static-files/9cf37b42-8164-4eff-9820-7504e5dc3c1f [last accessed March 2019].

[43] Stuckey M, Christensen B, Moulton-Meissner H. Out of thin air: assessing dispersion of *Mycobacterium chimaera* in the operating room. Abstract presented at: 67th Annual Epidemic Intelligence Service Conference, Atlanta, GA, April 17th, 2018.

[44] Walker JT, Lamagni T, Chand M. Evidence that *Mycobacterium chimaera* aerosols penetrate laminar airflow and result in infections at the surgical field. Lancet Infect Dis 2017;17:1019.

[45] Rosero CI, Shams WE. *Mycobacterium chimaera* infection masquerading as a lung mass in a healthcare worker. IDCases 2019;15:e00526.

[46] Baker AW, Lewis SS, Alexander BD, Chen LF, Wallace RJ, Jr, Brown-Elliott BA, et al. Two-phase hospital-associated outbreak of *Mycobacterium abscessus*: investigation and mitigation. Clin Infect Dis 2017;64:902–11.

[47] Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Resp Crit Care Med 2007;175:367–416.

[48] Hasse B. SY0821. Clinical management of *Mycobacterium chimaera* infection. ECCMID Austria. 2017. Available at: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=44559 [last accessed October 2019].

[49] Asadi T, Mullin K, Roselli E, Johnston D, Tan CD, Rodriguez ER, et al. Disseminated *Mycobacterium chimaera* infection associated with heater–cooler units after aortic valve surgery without endocarditis. J Thoracic Cardiovasc Surg 2018;155:2369–74.

[50] Schreiber PW, Hasse B, Sax H. *Mycobacterium chimaera* infections after cardiac surgery – lessons learned. Clin Microbiol Infect 2018;24:1117–18.

[51] 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 [Epub ahead of print].

[52] Boni C, Al-Sheikh M, Hasse B, Eberhard R, Kohler P, Hasler P, et al. Multimodal imaging of choroidal lesions in disseminated *Mycobacterium chimaera* infection after cardiothoracic surgery. Retina 2019;39:452–64.

[53] Brown CS, Smith CJ, Breen RA, Ormerod LP, Mittal R, Fisk M, et al. Determinants of treatment-related paradoxical reactions during anti-tuberculosis therapy: a case control study. BMC Infect Dis 2016;16:479.

[54] Phillips P, Bonner S, Gataric N, Bai T, Wilcox P, Hogg R, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005;41:1483–97.

[55] Wilson WR, Bower TC, Creager MA, Amin-Hanjani S, O'Gara PT, Lockhart PB, et al. Vascular graft infections, mycotic aneurysms, and endovascular infections: a scientific statement from the American Heart Association. Circulation 2016;134:e412–e60.

[56] Sah BR, Husmann L, Mayer D, Scherrer A, Rancic Z, Puippe G, et al. Diagnostic performance of 18F-FDG-PET/CT in vascular graft infections. Eur J Vasc Endovasc Surg 2015;49:455–64.

[57] Roque A, Pizzi MN, Cuellar-Calabria H, Aguade-Bruix S. (18)F-FDG-PET/CT angiography for the diagnosis of infective endocarditis. Curr Cardiol Rep 2017;19:15.

[58] Granados U, Fuster D, Pericas JM, Llopis JL, Ninot S, Quintana E, et al. Diagnostic accuracy of 18F-FDG PET/CT in infective endocarditis and implantable cardiac electronic device infection: a cross-sectional study. J Nucl Med 2016;57:1726–32.

[59] Orvin K, Goldberg E, Bernstine H, Groshar D, Sagie A, Kornowski R, et al. The role of FDG-PET/CT imaging in early detection of extra-cardiac complications of infective endocarditis. Clin Microbiol Infect 2015;21:69–76.

[60] Husmann L, Huellner MW, Ledergerber B, Anagnostopoulos A, Stolzmann P, Sah BR, et al. Comparing diagnostic accuracy of ^{18}F-FDG-PET/CT, contrast enhanced CT and combined imaging in patients with suspected vascular graft infections. Eur J Nucl Med Mol Imaging 2019;46:1359–68.

[61] Husmann L, Ledergerber B, Anagnostopoulos A, Stolzmann P, Sah BR, Burger IA, et al. The role of FDG PET/CT in therapy control of aortic graft infection. Eur J Nucl Med Mol Imaging 2018;45:1987–97.

[62] van Ingen J. Microbiological diagnosis of nontuberculous mycobacterial pulmonary disease. Clin Chest Med 2015;36:43–54.

[63] Inojosa WO, Minniti G, Scotton PG. Is *Mycobacterium chimaera* infection after cardiac surgery a risk factor for bacterial prosthetic valve endocarditis? Clin Infect Dis 2019 Jun 20 [Epub ahead of print].

[64] European Centre for Disease Prevention and Control. Protocol for case detection, laboratory diagnosis and environmental testing of *Mycobacterium chimaera* infections potentially associated with heater–cooler units. Available at: http://ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/about_programme.aspxEU [last accessed October 2019].

[65] Wallace RJ, Jr, 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;51:1747–52.

[66] Mok S, Rogers TR, Fitzgibbon M Evaluation of GenoType NTM-DR Assay for Identification of *Mycobacterium chimaera*. J Clin Microbiol 2017;55:1821–6.

[67] Lecorche E, Haenn S, Mougari F, Kumanski S, Veziris N, Benmansour H, et al. Comparison of methods available for identification of *Mycobacterium chimaera*. Clin Microbiol Infect 2018;24:409–13.

[68] Epperson LE, Timke M, Hasan NA, Godo P, Durbin D, Helstrom NK, et al. Evaluation of a novel MALDI biotyper algorithm to distinguish *Mycobacterium intracellulare* from *Mycobacterium chimaera*. Front Microbiol 2018;9:3140.

[69] Zozaya-Valdes E, Porter JL, Coventry J, Fyfe JA, Carter GP, da Silva AG, et al. A target-specific assay for rapid and quantitative detection of *Mycobacterium chimaera* DNA. J Clin Microbiol 2017;55:1847–56.

[70] Hasan NA, Epperson LE, Lawsin A, Rodger RR, Perkins KM, Halpin AL, et al. Genomic analysis of cardiac surgery-associated *Mycobacterium chimaera* infections, United States. Emerg Infect Dis 2019;25:559–63.

[71] Nomura J, Rieg G, Bluestone G, Townson Tsai T, Lai A, Dryjanski-Yanovsky J, et al. Rapid detection of invasive *Mycobacterium chimaera* infection by using a novel plasma-based next-generation sequencing assay. Open Forum Infect Dis 2017;4:S174.

[72] Nomura J, Rieg G, Bluestone G, Tsai T, Lai A, Terashita D, et al. Rapid detection of invasive *Mycobacterium chimaera* disease via a novel plasma-based next-generation sequencing test. BMC Infect Dis 2019;19:371.

[73] Chairs ASToIECGWC, Pettersson GB, Coselli JS, Writing C, Pettersson GB, Coselli JS, et al. 2016 The American Association for Thoracic Surgery (AATS) consensus guidelines: surgical treatment of infective endocarditis: executive summary. J Thoracic Cardiovasc Surg 2017;153:1241–58 e29.

[74] Deggim-Messmer V, Bloemberg GV, Ritter C, Voit A, Homke R, Keller PM, et al. Diagnostic molecular mycobacteriology in regions with low tuberculosis endemicity: combining real-time PCR assays for detection of multiple mycobacterial pathogens with line probe assays for identification of resistance mutations. EBioMedicine 2016;9:228–37.

[75] Marchetti G, Gori A, Catozzi L, Vago L, Nebuloni M, Rossi MC, et al. Evaluation of PCR in detection of *Mycobacterium tuberculosis* from formalin-fixed, paraffin-embedded tissues: comparison of four amplification assays. J Clin Microbiol 1998;36:1512–17.

[76] Zimmermann DR, Stadeli-Brodbeck R, Ajmo M, Dours-Zimmermann MT, Pfyffer GE, Heitz PU. [Molecular pathologic detection of mycobacteria.] Verh Dtsch Ges Pathol 1997;81:273–80.

[77] Koh WJ, Jeong BH, Jeon K, Lee SY, Shin SJ. Therapeutic drug monitoring in the treatment of *Mycobacterium avium* complex lung disease. Am J Resp Crit Care Med 2012;186:797–802.

[78] Morimoto K, Namkoong H, Hasegawa N, Nakagawa T, Morino E, Shiraishi Y, et al. Macrolide-resistant *Mycobacterium avium* complex lung disease: analysis of 102 consecutive cases. Ann Am Thorac Soc 2016;13:1904–11.

[79] Brown-Elliott BA, Nash KA, Wallace RJ, Jr. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. Clin Microbiol Rev 2012;25:545–82.

[80] van Ingen J, Totten SE, Helstrom NK, Heifets LB, Boeree MJ, Daley CL. In vitro synergy between clofazimine and amikacin in treatment of nontuberculous mycobacterial disease. Antimicrob Agents Chemother 2012;56:6324–7.

[81] Koh WJ, Hong G, Kim SY, Jeong BH, Park HY, Jeon K, et al. Treatment of refractory *Mycobacterium avium* complex lung disease with a moxifloxacin-containing regimen. Antimicrob Agents Chemother 2013;57:2281–5.

[82] 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;25:379.e1–379.e7.

[83] Ruth MM, Sangen JJN, Remmers K, Pennings LJ, Svensson E, Aarnoutse RE, et al. A bedaquiline/clofazimine combination regimen might add activity to the treatment of clinically relevant non-tuberculous mycobacteria. J Antimicrob Chemother 2019;74:935-943.

[84] Philley JV, Wallace RJ, Jr., Benwill JL, Taskar V, Brown-Elliott BA, Thakkar F, et al. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. Chest 2015;148:499–506.

[85] 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;68:1137–9.

[86] Griffith DE, Brown-Elliott BA, Shepherd S, McLarty J, Griffith L, Wallace RJ, Jr. Ethambutol ocular toxicity in treatment regimens for *Mycobacterium avium* complex lung disease. Am J Resp Crit Care Med 2005;172:250–3.

[87] Magis-Escurra C, Alffenaar JW, Hoefnagels I, Dekhuijzen PN, Boeree MJ, van Ingen J, et al. Pharmacokinetic studies in patients with nontuberculous mycobacterial lung infections. Int J Antimicrob Agents 2013;42:256–61.

[88] 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 Resp Crit Care Med 2012;186:559–65.

[89] Jeong BH, Jeon K, Park HY, Moon SM, Kim SY, Lee SY, et al. Peak plasma concentration of azithromycin and treatment responses in *Mycobacterium avium* complex lung disease. Antimicrob Agents Chemother 2016;60:6076–83.

[90] Woods GL. Susceptibility testing of mycobacteria, Nocardia spp., and other aerobic actinomycetes, 3rd edition. CLSI document M24Ed3. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

[91] Woods GL. Performance standards for susceptibility testing of mycobacteria, nocardia spp. and other aerobic actinomycetes. CLSI doument M62Ed1. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

[92] Nikolayevskyy V, Maurer FP, Holicka Y, Taylor L, Liddy H, Kranzer K. Novel external quality assurance scheme for drug susceptibility testing of non-tuberculous mycobacteria: a multicentre pilot study. J Antimicrob Chemother 2019;74:1288–94.

[93] Woods GL. Susceptibility testing of mycobacteria, nocardia, and other aerobic actinomycetes; approved standard. CLSI document M24-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

[94] Woods GL. Susceptibility testing of mycobacteria, nocardia and other aerobic actinomycetes; approved standard. NCCLS document M24-A. Wayne, PA: National Committee for Clinical Laboratory Standards; 2003.

[95] Mok S, Hannan MM, Nolke L, Stapleton P, O'Sullivan N, Murphy P, et al. Antimicrobial susceptibility of clinical and environmental *Mycobacterium chimaera* Isolates. Antimicrob Agents Chemother 2019;63.

[96] Brown-Elliott BA, Iakhiaeva E, Griffith DE, Woods GL, Stout JE, Wolfe CR, et al. In vitro activity of amikacin against isolates of *Mycobacterium avium* complex with proposed MIC breakpoints and finding of a 16S rRNA gene mutation in treated isolates. J Clin Microbiol 2013;51:3389–94.

[97] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195–283.

[98] Jarashow MC, Terashita D, Balter S, Schwartz B. Notes from the field: *Mycobacteria chimaera* infections associated with heater–cooler unit use during cardiopulmonary bypass surgery – Los Angeles County, 2012–2016. Morb Mortal Wkly Rep 2019;67:1428–9.

[99] Centers for Disease Control and Prevention. CDC advises hospitals to alert patients at risk from contaminated heater–cooler devices used during cardiac surgery. October 13th, 2016.

[100] Marra AR, Diekema DJ, Edmond MB. *Mycobacterium chimaera* infections associated with contaminated heater–cooler devices for cardiac surgery: outbreak management. Clin Infect Dis 2017;65:669–74.

[112] 101Allen KB, Yuh DD, Schwartz SB, Lange RA, Hopkins R, Bauer K, et al. Nontuberculous *Mycobacterium infections* associated with heater–cooler devices. Ann Thorac Surg 2017;104:1237–42.

[107] Barker TA, Dandekar U, Fraser N, Dawkin L, Sweeney P, Heron F, et al. Minimising the risk of *Mycobacterium chimaera* infection during cardiopulmonary bypass by the removal of heater–cooler units from the operating room. Perfusion 2018;33:264–9.

[103] Percival SL, Suleman L, Vuotto C, Donelli G. Healthcare-associated infections, medical devices and biofilms: risk, tolerance and control. J Med Microbiol 2015;64:323–34.

[104] Gotting T, Klassen S, Jonas D, Benk C, Serr A, Wagner D, et al. Heater–cooler units: contamination of crucial devices in cardiothoracic surgery. J Hosp Infect 2016;93:223–8.

[105] 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;96:209–20.

[106] Garvey MI, Bradley CW, Walker J. A year in the life of a contaminated heater–cooler unit with *Mycobacterium chimaera*? Infect control hosp epidemiol 2017;38:705–11.

[107] Mertz D, Macri J, Hota S, Amaratunga K, Davis I, Johnston L, et al. Response to alert on possible infections with *Mycobacterium chimaera* from contaminated heater–cooler devices in hospitals participating in the Canadian Nosocomial Infection Surveillance Program (CNISP). Infect Control Hosp Epidemiol 2018;39:482–4.

[108] Ogunremi T, Taylor G, Johnston L, Amaratunga K, Muller M, Coady A, et al. *Mycobacterium chimaera* infections in post-operative patients exposed to heater–cooler devices: an overview. Can Commun Dis Rep 2017;43:107–13.

[109] Food and Drug Administration. Update: availability of deep-cleaning service of certain LivaNova PLC (formerly Sorin Group Deutschland GmbH) Stöckert 3T heater–cooler

systems in the U.S.: FDA Safety Communication. 2018. Available at: https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm610394.htm [last accessed March 2019].

[110] Casini B, Tuvo B, Totaro M, Baggiani A, Privitera G. Detection and decontamination of *Mycobacterium chimaera* and other non-tuberculosis mycobacteria in heater–cooler devices used in cardiopulmonary bypass: a manufacturer and national guidelines summary, and a potential resolution to the problem requiring further investigation. Perfusion 2019 Aug 30 [Epub ahead of print].

[111] Food and Drug Administration. Updated information to reduce potential cardiac surgery infection risks associated with the LivaNova 3T heater–cooler systems: FDA Safety Communication. October 19th, 2018.

[112] Schreiber PW, Kohler 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;99:284–9.

[113] Diekema DJ. *Mycobacterium chimaera* infections after cardiovascular surgery: lessons from a global outbreak. Trans Am Clin Climatol Assoc 2019;130:136–44.

[114] Sargent HM, Crouch GC, Roberts S, Finucane AK. Prosthetic conduit endocarditis with nontuberculous mycobacteria in a child: associated with the water mattress and heater chiller unit. World J Pediatr Congenit Heart Surg 2019 May 15 [Epub ahead of print].

[115] Burgess W, Margolis A, Gibbs S, Duarte RS, Jackson M. Disinfectant susceptibility profiling of glutaraldehyde-resistant nontuberculous mycobacteria. Infect Control Hosp Epidemiol 2017;38:784–91.

[116] Nagpal A, Wentink JE, Berbari EF, Aronhalt KC, Wright AJ, Krageschmidt DA, et al. Cluster of *Mycobacterium wolinskyi* surgical site infections at an academic medical center. Infect Control Hosp Epidemiol 2014;35:1169–75.

Table Ia

Evidence-based scoring system (adapted from [31])

Classes of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful	Is not recommended

Table Ib

Levels of evidence (adapted from [31])

Level of evidence A	Data derived from multiple, randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Table II

Cardiovascular surgical procedures at risk of *Mycobacterium chimaera* infections

Procedure	Class	Level
Cardiopulmonary bypass surgery involving a 3T-HCD and one or more of the following: – Prosthetic material used for cardiac valve or aortic repair [7,21][a] – Mechanical circulatory support device implantation [19] – Implant of palliative shunts, conduits or other prostheses for congenital heart disease (CHD) [7,20,49] – Coronary artery bypass grafting [9,30][b] – Heart transplantation [13]	IIa	C

[a]Aortic surgery is reported to have the highest risk [14].

[b]Coronary artery bypass grafting bears the lowest risk [9,30].

Table III

Classification of choroidal lesions based on multi-modal imaging (adapted from [52])

Imaging modality	Active lesion	Inactive lesion in regression
Fundus photography		
Shape	Ovoid to round	Ovoid to round
Border	Indistinct	Well-defined
Size	Small (<1 disc diameter)	Small (<1 disc diameter)
Colour	Yellow–white	Whitish[a]
Fluorescein angiography		
Early	Hypofluorescent	Hyperfluorescent
Late	Hyperfluorescent	Hyperfluorescent
Indocyanine green angiography	Hypofluorescent	Hypofluorescent
Fundus autofluorescence	Hyperautofluorescent	Hypoautofluorescent
EDI-OCT		
Shape	Full-thickness, round, well-defined borders	Poorly defined margins
Internal reflectivity	Hyporeflective	Similar to the choroid
Transmission effect	Increased	Increased

EDI-OCT, spectral-domain optical coherence tomography including enhanced depth imaging.

[a]Pigmentation might develop and would be a sign of inactivity, but has not been observed so far.

Table IV

Proposed screening and follow-up examinations for patients with suspected or confirmed *Mycobacterium chimaera* ocular infection (adapted from [52])

Timepoint	Imaging modalities	Class	Level
Baseline ocular examination	Complete ophthalmic examination Visual acuity Intraocular pressure measurement Anterior and posterior segment slit-lamp examination including dilated fundus biomicroscopy Multi-modal imaging testing Wide-angle fundus photography FA/ICGA (if possible, by using a wide-angle camera) FAF EDI-OCT OCTA (if available)	IIa	C
Follow-up ocular examinations			
Absence of active ocular disease or Discontinuation of mycobacterial therapy	Clinical follow-up visits every 2 months with dilated fundus[a] Multi-modal imaging tests every 4 months[a]	IIb	C
Presence of active ocular disease[b]	Clinical follow-up visits every month with dilated fundus examination Multi-modal imaging tests every 2 months	IIb	C

EDI-OCT, spectral-domain optical coherence tomography including enhanced depth imaging; FAF, fundus autofluorescence imaging; FA/ICGA, fluorescein angiography/indocyanine green (ICG) angiography; OCTA, optical coherence tomography angiography.

[a]After one year of quiescence, the follow-up intervals might be extended to 3 and 6 months, respectively.

Table V

Diagnostic criteria of disseminated *Mycobacterium chimaera* infection (adapted from [7])

Exposure assessment	History of surgery requiring cardiopulmonary bypass surgery prior to symptoms of infection
Laboratory assessment	
Culture[a,b]	*M. chimaera*[*]-positive cultures obtained from a sterile site (blood, purulent material, tissue biopsy, or implanted prosthetic material). Mycobacterial blood cultures (BacTec myco Lytic/F bottles BD Bioscience); VersaTrek (Thermo Fisher) use of Isolator tubes (Isolator 10, Oxoid; Isostatw System, Wampole^{TM}) can either be directly inoculated at the point-of-care if the laboratory is on site or alternatively citrate/heparin blood should be sent to a mycobacteriology laboratory in case blood culture bottles are not available.
PCR[c]	Mycobacterium genus-specific PCR obtained from an invasive sample (blood, purulent material, tissue biopsy, or implanted prosthetic material).
Clinical assessment[d]	
Cardiovascular manifestations	Prosthetic valve endocarditis
	Prosthetic vascular graft infection
	Myocarditis
	Pseudoaneurysm formation
Localized infections	Sternotomy wound infection
	Mediastinitis
Extrathoracic manifestations[e]	Bloodstream infection and disseminated infection including embolic and immunologic manifestations
	Splenomegaly
	Bone marrow involvement with cytopenia
	Bone infection (arthritis, osteomyelitis)
	Pneumonitis
	Hepatitis
	Nephritis

	Skin infection
	Chorioretinitis
	Cerebral vasculitis
Constitutional symptoms	Fever
	Fatigue
	Weight loss
	Night sweats
	Joint pain
	Shortness of breath
	Infants: failure to thrive/febrile episodes
Histopathology[f]	Detection of non-caseating granuloma and foamy/swollen macrophages with/without acid fast bacilli in cardiac tissue in the proximity of the prosthetic material

PCR, polymerase chain reaction.

[a]Collect three heparin blood cultures.

[b]Tissue and bone acid-fast staining and mycobacterial cultures and acid-fast staining recommended. Submission to laboratory in native, aseptic container. Positive cultures identified as *M. avium* complex micro-organisms should undergo 16S rDNA (or alternatives such as hsp65/ITS) gene sequencing for species identification.

[c]Perform a mycobacterium genus-specific PCR or, if available, an *M. chimaera*-specific PCR. The species-specific PCR is likely more sensitive than a mycobacterium genus-specific PCR.

[d]Based on current evidence, asymptomatic individuals with previous open cardiac surgery should not undergo testing for *M. chimaera*.

[e]*M. chimaera* positive isolates should be whole genome sequenced in order to confirm relatedness to the global outbreak strain [28]. If a laboratory confirms the organism's identity is consistent with the outbreak strain, it is recommended that healthcare authorities be informed.

[f]Once a post-cardiopulmonary bypass *M. chimaera* infection is diagnosed at a hospital, providers should review every diagnosis of sarcoidosis, fever of unknown origin, and unknown vasculitis to exclude *M. chimaera* infection [15].

Confirmed cases: meet clinical and exposure criteria AND *M. chimaera* is detected by culture and PCR identification from invasive sample (blood, purulent material, biopsy or prosthetic material).

Probable cases: meet clinical and exposure criteria AND *M. chimaera* is detected by PCR not by culture from invasive sample (blood, purulent material, biopsy or prosthetic material)

operating theatre OR *M. avium* complex is detected by culture and PCR identification from invasive sample (blood, purulent material, biopsy or prosthetic material) OR detection of non-caseating granuloma and foamy/swollen macrophages with acid-fast bacilli in cardiac tissue in the proximity of the prosthetic material or in specimen from sternotomy wound.

Table VI

Potential regimens for the antimicrobial treatment of *Mycobacterium chimaera* infection

Type of *Mycobacterium chimaera* strain	Suggested regimen	Class	Level
Wild-type *Mycobacterium chimaera*			
First-line therapy	Azithromycin, rifampin (rifabutin), ethambutol, amikacin[a]	I	C
Second-line therapy	Clarithromycin, rifabutin (rifampin), ethambutol, amikacin[a]	I	C
Drug-resistant *M. chimaera*[b]			
Clarithromycin	Rifabutin/rifampin, ethambutol, amikacin, clofazimine[b,c,d]	I	C
Amikacin	Clarithromycin, rifabutin/rifampin, ethambutol, clofazimine[c,d]		

[b]Consider repeat testing since resistances are rare. Providers should seek expert consultation in all these cases.

[a]Amikacin is recommended and should be continued as long as it is tolerated via peripherally inserted central catheter (PICC) as outpatient parenteral antibiotic therapy (OPAT) (Class IIa, Level C).

[c]Adding clofazimine as an additional antimicrobial agent may be considered (Class IIb, Level C). There is an in-vitro synergy for clofazimine and amikacin [80].

[d]Any other medication (moxifloxacin, linezolid, bedaquiline) should be administered after expert consultation and if resistance test results from reference laboratories are available.

Table VII

Drugs used in the management of adult patients with *Mycobacterium chimaera* infection, recommended dosages, route and common adverse drug reactions

Antibiotic	Dosage[a]	Route	Comments/side-effects
Azithromycin	250–500 mg qd[b] or 500 mg 3× per week	Oral/IV	May prolong QTc interval. Reversible hearing impairment. Diarrhoea. Toxicities are dose- and serum-level-related.
Clarithromycin	500 mg bid[b]	Oral/IV	May prolong QTc-interval. Frequent gastrointestinal toxicities like metallic taste, diarrhoea, nausea, vomiting and elevated liver function tests. Toxicities are dose- and serum-level-related.
Ethambutol	15 mg/kg body weight qd 25 mg/kg 3× per week[c]	Oral	Retrobulbar optic neuritis with visual loss; baseline and as needed testing of visual acuity and colour discrimination (Ishihara tests) is recommended as well as careful instructions to patient[d]
Rifampin	600 mg qd	Oral/IV	Monitor for hepatotoxicity; drugs metabolized by cytochrome P-450 may require dose adjustments (e.g. macrolides, oral contraceptives, methadone, warfarin, and ART). Gastrointestinal reactions are common; orange discoloration of bodily fluids. Hypersensitivity reaction.
Rifabutin	150–300 mg qd or 150–300 mg 3× per week[e]	Oral/IV	Monitor for hepatotoxicity; drugs metabolized by cytochrome P-450 may require dose adjustments (e.g. macrolides, oral contraceptives, methadone, warfarin, and ART). Fever. Anterior uveitis; bone marrow suppression; pseudojaundice (skin discoloration with normal bilirubin); polyarthralgias; ‘flu-like’ illness.
Amikacin	15 mg/kg qd[f] or	IV	Monitoring of renal function and vestibular/hearing function necessary. TDM required.

	25 mg/kg 3× per week		
Companion drugs (not clearly proven efficacy)			
Clofazimine	100–200 mg qd	Oral	May prolong QTc interval. Consider reduction of dosage to 5× per week in case of severe skin discoloration. Skin discoloration is usually reversible. Abdominal pain and/or eye symptoms.
Bedaquiline	Weeks 1+2: 400 mg qd Weeks 3–24: 200 mg 3× per week	Oral	Take with food. Electrolyte abnormalities, hepatotoxicity, pancreatitis, myopathy. May prolong QTc interval, especially when concurrently used with moxifloxacin. Very little efficacy data [84].
Moxifloxacin	400 mg qd	Oral/IV	Gastrointestinal disturbance: nausea and bloating. Neurologic effects: dizziness, insomnia, tremulousness, and headache. May prolong QTc interval. Very little efficacy data [81].
Linezolid[b]	600 mg qd/bid	Oral/IV	Risk of lactic acidosis, bone marrow suppression, and neurological toxicity (peripheral neuropathy).

qd, once daily; bid, twice a day; tid, three times a day; qid, four times a day; IV, intravenous; ART, antiretroviral therapy; TDM, therapeutic drug monitoring.

[a]Dosage may need adjustment with age, body weight.

[b]Be aware of drug–drug interactions with rifamycins. In case of combination therapy of azithromycin with rifampicin the 250 mg qd dosage of azithromycin might be too low [88,89].

[c]Ethambutol dose for older patients may be reduced to daily 25 mg/kg due to toxicity.

[d]Refer to ophthalmologists if optic neuritis suspected.

[e]A dose reduction of rifabutin 150–300 mg 3× per week may be considered if daily treatment is not well tolerated.

[f]In case of long-term treatment, a reduction of dosage to 7 mg/kg per dose may be considered. Alternative dosage three times weekly, especially for patients aged >60 years.

Table VIII

Recommendations on the perioperative management of *Mycobacterium chimaera*-infected patients

Recommendation	Class	Level
Perform coronary angiography and intraoperative echocardiography	I	C
– Antimicrobial treatment	IIa	C
– The usual surgical perioperative prophylaxis for cardiac procedures is recommended [97]		
– Continue *M. chimaera* treatment perioperatively	I	C
Pre- and post-anaesthesia care unit		
– No isolation precautions in the pre- and post-anaesthesia care unit	I	C
– Schedule subsequent operations at least 30 min later to facilitate an OR 'wash-out phase' may be considered	IIb	C
– Change the filters and the anaesthetic tubing and the use of a mycobactericidal oxidizing disinfectant may be considered [115]	IIb	C
– To potentially avoid theoretical airway colonization in subsequent patients, consider processing the warming device	IIb	C
– Frequent staff turnover for breaks of nurses, scrub technicians and anaesthesia is not recommended	III	C
– Change of clothes or wearing of paper gowns over scrub clothing to be discarded later is not recommended	III	C

OR, operating room.

Table IX

Factors likely associated with *Mycobacterium chimaera* relapses[a]

Delayed antimycobacterial treatment
No ‘lead-in’ preoperative antimycobacterial treatment
Positive *M. chimaera* valve culture
Cardiac or extrathoracic prosthetic material
Disseminated disease with distant foci and abscess formation
Macrolide and/or amikacin resistant *M. chimaera* strain

[a]These factors are based on expert consensus.

Table X

Recommendations for *Mycobacterium chimaera* infection patient/provider notification, additional case-finding and investigation, and screening

Recommendation	Class	Level
• Patient notification should be considered. However, to date, such notifications have not contributed substantially to case-finding. Discussion and input by health department authorities and likely consumer stakeholders needed.	IIa	C
• Provider notification should be considered and has been successful in case detection. *M. chimaera* infection can occur among patients with open-heart surgery with CPB after 2008 (earliest sentinel surgery) and before the introduction of effective risk mitigation measures.	IIa	C
• Additional case-finding through evaluation and testing of patients with a history of exposure to (3T-)HCD (past 5–6 years) should be restricted to those who are symptomatic and/or have at least one of the following: – Culture-negative prosthetic valve endocarditis – Culture-negative aortic graft infection – Mechanical circulatory support device infection – Culture-negative sternal osteomyelitis and/or mediastinitis – Fever of unknown origin – Vasculitis – Undetermined systemic disease, sarcoidosis-like or other granulomatous disease	IIa	C
• Diagnostic measures: – Physical examination including ophthalmoscopy, medical history (weight loss, night sweats, fever, skeletal pain, etc.), blood tests (ESR, CRP, complete blood count, transaminases, creatinine) – Mycobacterial blood cultures (BacTec myco Lytic/F bottles BD Bioscience); VersaTrek (Thermo Fisher) use of Isolator tubes (Isolator 10, Oxoid; Isostatw System, Wampole™). – Tissue mycobacterial cultures, broad range and mycobacterium-genus specific PCR and histopathological work-up in case of reoperative heart surgery or surgery of distant foci.	I	C
• Additional case-finding tools:	IIb	C

– Review non-respiratory *M. avium* complex isolates and identify patients with former CPB with the use of 3T-HCD within 5–6 years. – Review culture-negative prosthetic valve endocarditis/aortic graft infections and histopathology reports for manifestations compatible with a probable post-cardiac-surgery *M. chimaera* disease. – Review sarcoidosis cases with former CPB with former CPB within 5–6 years. – Review histopathology reports from excised heart valves/aortic grafts for granulomatous tissue formation.		
• Routine screening of asymptomatic patients with a history of exposure to (3T-)HCD is not recommended.	III	C

HCD, heater–cooler device; CPB, cardiopulmonary bypass; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction.

Table XI

Prevention of future *Mycobacterium chimaera* exposure

Topic	Recommendations	Class	Level
General guidelines for HCDs			
HCD traceability	Register HCD, patient, and date of use [33]	I	C
Water safety	Use only sterile or all-bacteria-filtered-water (0.22 mm or less) including when making ice needed for patient cooling [101]	IIa	C
Use cleaning and disinfection procedures according to the manufacturer	Maintain log of cleaning and disinfection. Caveat: Current decontamination protocols may be insufficient due to biofilm formation by mycobacteria in the implicated devices [41,102]. Biofilm formation can be seen by discoloration/cloudiness in the fluid lines or circuits [101].	I	C
Separate HCD (other than 3T) exhaust air from OR[a]	Separation of HCDs from air volume of critical medical areas such as operating rooms may be considered.	IIb	C
Remove/replace contaminated 3T-HCD from service	All 3T-HCDs manufactured should ideally be removed from service or alternatively measures ensuring strict separation between air in the OR and the potentially contaminated air around HCD should be taken.	I	C
Separate 3T-HCD exhaust air from OR	Guarantee strict separation of HCDs from air volume of	I	C

	critical medical areas such as operating rooms [35,102]. Place HCD outside the OR, whenever possible. Encase HCD connected to the OR exhaust.		
Testing of HCD			
Non-tuberculous mycobacterium surveillance	Use the 'Protocol for case detection, laboratory diagnosis and environmental testing of *M. chimaera* infections potentially associated with heater–cooler units' by ECDC [64].	IIa	C

OR, operating room; HCD, heater–cooler device; CPB, cardiopulmonary bypass; ECDC, European Centre for Disease Prevention and Control.
[a]Although contamination of other device types with *M. chimaera* has been described, no case of infection has been linked to other device types neither is there evidence of aerosolization with other device types in limited investigations so far [28].

Figure 1. Algorithm for microbiological diagnosis of suspected cardiovascular infections including possible *Mycobacterium chimaera* infections (adapted from [31]). *Among patients meeting exposure criterion and a having a suggestive clinic, consider upfront AFB cultures. AFB, acid-fast bacilli; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; PCR, polymerase chain reaction; ITS, internal transcribed spacer region.