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Guidelines

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

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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.

Background

Mycobacterium chimaera is an environmental, slowly-growing non-tuberculous mycobacterium (NTM) [1] and, until recently, would have been identified by most clinical

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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, United Kingdom) 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.

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 to i) provide an update on *M. chimaera* epidemiology and risk factors, ii) develop guidelines for diagnosis and management in individual patients, and iii) 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 [31] was included in the novel recommendations designated herein (Table Ia and Ib).

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 taskforce 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 if 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]. We searched Medline 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.

Epidemiology and risk factors

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 infections that complicate open-chest surgeries with CPB including deep sternal surgical site infections, 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

Table Ia
Evidence based scoring system*

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

Adapted from reference [31].

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Table Ib
Levels of evidence

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

Adapted from reference [31].

cases/14,045 patients with valve procedures, resulting in 0.78 cases/1,000 procedures (95% CI 0.41—1.45) [32]. In the United Kingdom, 16 cases in 112,644 patients with open-chest procedures were initially identified, resulting in 0.14 cases/1,000 procedures (95% CI 0.08—0.23) [8]. In the United States, numerous hospital-specific prevalence rates range from 1/1000 to 1/10,000 [26]. Given the long incubation periods and observed change in risk [8], 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.

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 HCDs, 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 [6], 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. 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 minute 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* infections has been reported among exposed operating room 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 (eg. 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 masks 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].

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. Notably, 3T-HCD 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 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.

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Table II
Cardiovascular surgical procedures at risk of *M. chimaera* infections

Procedure	Class	Level
Cardiopulmonary bypass surgery involving a 3THCD 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][3] • Coronary artery bypass grafting [9,30][b] • Heart transplantation [13]	IIa	C

Note.
[a] Aortic surgery is reported to have the highest risk [14].
[b] Coronary artery bypass grafting bears the lowest risk [9,30].

Multidisciplinary hospital patient management

Recommendations

- 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 PET/CT 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, anti-mycobacterial 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 anesthesiologist are warranted to determine optimal timing of surgery once a surgical indication is recognized.

Diagnosis of *M. chimaera* infection

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 6 weeks to more than 5 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 surgical site infection, 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 surgical site infections [8,13,14] or mediastinitis [8,16]. Disseminated (extrathoracic) manifestations with bacteremia 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 involvement [7]. 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 can 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 cytopenias (anemia, leukocytopenia, and/or thrombocytopenia [7,15]) or hemophagocytic 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 AFB smears. Some patients also develop neurological complications with vasculitis of the brain, encephalitis or chorioretinitis [7,15,51].

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

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presence of complications like 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 multimodal 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.

Immune reconstitution inflammatory response syndrome

An immune reconstitution inflammatory syndrome (IRIS) can complicate tuberculosis treatment with a variety of clinical tuberculosis manifestations, with 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 anti-mycobacterial therapy. Currently, the long-term outcome and the spectrum of disease of potential *M. chimaera*-related IRIS are yet to be fully defined.

Table III

Classification of choroidal lesions based on multimodal imaging (adapted [52])

Imaging modality	Active lesion	Inactive lesion 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)
Color	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

Abbreviation: EDI-OCT, Spectral-domain optical coherence tomography including enhanced depth imaging.

Note:

[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 *M. chimaera* ocular infection (adapted [52])

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

Abbreviations: 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.

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Imaging techniques

Recommendations

- Transesophageal echocardiogram for detection of cardiac vegetations, aortic root collections, and evaluation of valvular function is recommended (Class I, Level C).
- PET/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 ^{18}F-fluorodeoxyglucose positron emission tomography (PET) with computed tomography (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].

Microbiological diagnosis

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 material (e.g. heparin or sodium citrate blood send for mycobacterial cultures) need to be used. A positive acid-fast bacilli (AFB) culture for mycobacteria from a specimen taken from a sterile extra-pulmonary site (blood, purulent material, bone marrow, tissue, or implanted prosthetic material) should be considered a suspect case. If there is no mycobacterial growth after 8 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 (Thermofisher, Cleveland, OH, USA) should be used to maximize sensitivity [62]. Of note, according to a recent case series of 30 patients with *M. chimaera* in the UK [9], 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. 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].

Molecular diagnosis

Most laboratory methods identify a *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 6–10 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 [65], albeit rarely available in clinical laboratories. 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, Thermofisher, Foster City, CA).

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 (MALDI-TOF-ms) 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.

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 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 4 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

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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 (Thermofisher, formerly Trek Diagnostics, Cleveland, OH) use of Isolator tubes (Isolator 10, Oxoid; Isostatw System, WampoleTM) 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

Confirmed cases Meet clinical and exposure criteriaAND- *M. chimaera* is detected by culture and polymerase chain reaction (PCR)identification from invasive sample (blood, purulent material, biopsy or prosthetic material).

Probable cases Meet clinical and exposure criteriaAND- *M. chimaera* is detected by polymerase chain reaction (PCR) not by culture from frominvasive sample (blood, purulent material, biopsy or prosthetic material) operating theatreOR*M. avium* complex (MAC) is detected by culture and polymerase chain reaction(PCR) identification from invasive sample (blood, purulent material, biopsy or prosthetic material).OR- Detection of non-caseating granuloma and foamy/swollen macrophages with acidfast bacilli in cardiac tissue in the proximity of the prosthetic material or inspecimen from sternotomy wound.

[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 microorganisms 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, a *M. chimaera*-specific PCR. The species-specific PCR is like 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 health care authorities be informed.

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

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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 world-wide 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].

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 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).
- Acid-fast bacilli 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 (NGS) 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 fever of unknown origin (FUO), if initial mycobacteria 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. Most of the time 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 7–10 days, while 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.

Histopathological diagnosis of M. chimaera infection

Recommendation

- 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. Acid-fast bacilli 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 acid-fast bacilli 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 microorganisms 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].

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 [31] are not applicable in these patients. Moreover, sporadic cases with bacteremia and disseminated infections without obvious signs of valve involvement have occurred [3,49].

Antimicrobial therapy

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 as long as tolerated via peripherally inserted central catheter (PICC) as outpatient parenteral antibiotic therapy (OPAT)

(Class IIa, Level C).

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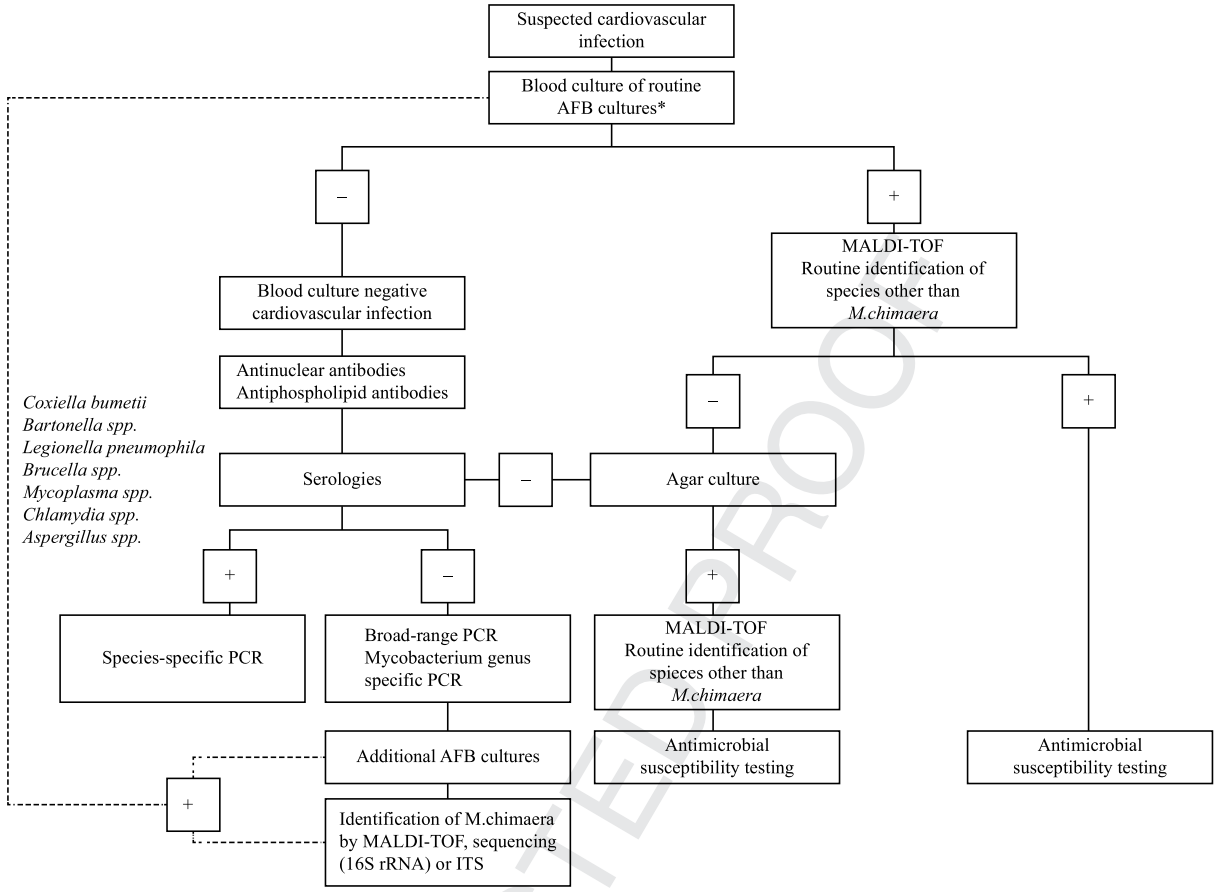

Figure 1. An algorithm for microbiological diagnosis of suspected cardiovascular infections including possible *M. chimaera* infections. Abbreviations: IE, infective endocarditis; PCR, polymerase chain reaction; AFB, acid fast bacilli; MALDI-TOF, Matrix-assisted laser desorption ionization time-of-flight (adapted from [31]). Note: *Among patients meeting exposure criterion and a having a suggestive clinic consider upfront AFB cultures.

Table VI displays 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 the rifamycins are less [77] and the azithromycin tolerability is in general better than 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 twelve 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.

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).

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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[b]	I	C
Second line therapy	Clarithromycin, rifabutin (rifampin), ethambutol, amikacin[b]	I	C
Drug-resistant *Mycobacterium chimaera*[a]			
Clarithromycin	Rifabutin/rifampin, ethambutol, amikacin, clofazimine[b,c,d]	I	C
Amikacin	Clarithromycin, rifabutin/rifampin, ethambutol, clofazimine [c,d]		

Notes.
[a] Consider repeat testing since resistances are rare. Providers should seek expert consultation in all of these cases.
[b] Amikacin is recommended and should be continued as long as 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 given after expert consultation and if resistance test results from reference laboratories available.

- Periodic ophthalmologic examinations with visual acuity, red-green color 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 makrolides, quinolones, clofazimine, linezolid and bedaquline (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. Anti-mycobacterial antibiotics with *M. chimaera* activity and their more common adverse drug reactions are listed in Table VII. Auditory and vestibular function can 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 color 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].

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 antimicrobial susceptibility testing (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 redefined in the M24Ed3 [90] and M62Ed1 [91] CLSI documents, respectively. To insure 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

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

Antibiotic	Dosage[f]	Route	Comments/Side effects
Azithromycin	250–500 mg qd[a] Or 500 mg 3x/per week	Oral/IV	May prolong QTc-interval. Reversible hearing impairment. Diarrhea. Toxicities are dose and serum-level related.
Clarithromycin	500 mg bid[a]	Oral/IV	May prolong QTc-interval. Frequent gastrointestinal toxicities like metallic taste, diarrhea, nausea, vomiting and elevated liver function tests. Toxicities are dose and serum-level related.
Ethambutol	15 mg/kg body weight qd 25mg/kg 3x/per week[c]	Oral	Retrobulbar optic neuritis with visual loss; Baseline and as needed testing of visual acuity and color discrimination (Ishihara tests) is recommended as well as careful instructions to patient[e]
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 x/per week[d]	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[b] Or 25 mg/kg 3x/per week	IV	Monitoring of renal function and vestibular/hearing function necessary. TDM required.
Companion drugs (not clearly proven efficacy)			
Clofazimine	100–200 mg qd	Oral	May prolong QTc-interval. Consider reduction of dosage to 5 times/week in case of severe skin discoloration. Skin discoloration is usually reversible. Abdominal pain and/or eye symptoms.
Bedaquiline	Week 1+2: 400 mg qd Week 3–24: 200 mg 3x/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[a]	600 mg qd/bid	Oral/IV	Risk of lactic acidosis, bone marrow suppression, and neurological toxicity (peripheral neuropathy)

Abbreviations: 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.
Note:
[a] 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].
[b] 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 >60 years of age.
[c] Ethambutol dose for older patients may be reduced to daily 25 mg/kg due to toxicity.
[d] A dose reduction of rifabutin 150–300 mg 3x/week may be considered if daily treatment is not well tolerated.
[e] Refer to ophthalmologists if optic neuritis suspected.
[f] Dosage may need adjustment with age, body, weight.

resistance has been recovered [7,15,82]. One patient who received prolonged macrolide treatment and suffered infection relapse, had an isolate that demonstrated intermediate resistant to clarithromycin (MIC of ≥16 μg/ml to ≥32 μg/ml depending on pH) [52].

Routine susceptibility testing of anti-mycobacterial 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 (≤16 mg/L susceptible, 32 mg/L intermediate, and ≥64 mg/L resistant) [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].

Surgical intervention

Pre- and perioperative management

Recommendations on the perioperative management and the hospital epidemiology precautions for patients who require

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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 surgical site infection 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-anesthesia care unit are not required.

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 anti-mycobacterial 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 centers advise preoperative anti-mycobacterial therapy for 6–12 weeks to reduce the chance of planktonic forms seeding replacement devices [7,49]. Whether anti-mycobacterial 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 anti-mycobacterial therapy. In some cases, surgical intervention at non-cardiovascular infection sites will also be required.

Table VIII
Recommendations on the perioperative management of *M. 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-anesthesia care unit	I	C
• No isolation precautions in the pre- and post-anesthesia care unit	IIb	C
• Schedule subsequent operations at least 30 minutes later to facilitate an OR "wash out phase" may be considered.	IIb III	C C
• Change the filters and the anesthetic tubing and the use of a mycobactericidal oxidizing disinfectant may be considered [115].	III	C
• To potentially avoid theoretical airway colonization in subsequent patients, consider processing the warming device		
• Frequent staff turnover for breaks of nurses, scrub techs and anesthesia is not recommended.		
• Change of clothes or wearing of paper gowns over scrub clothing to be discarded later is not recommended.		

Abbreviation: OR operating room.

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 anti-mycobacterial therapy to determine if cure of infection has been achieved. Among the few reported survivors with defined follow-up [7,9], the relapse rate has been as high as 30–50%. 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*

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Table IX
Factors likely associated with *M. chimaera* relapses.[a]

Delayed anti-mycobacterial treatment
No 'lead-in' pre-operative anti-mycobacterial 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

Note:
[a] These factors are based on expert consensus

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].

Considerations for patient notification, screening and investigation

Recommendation

- 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 5th year anniversary of their surgery, so that patients can seek medical care if warning signs and symptoms of a *M. chimaera* infection develop. Given the higher yield among hospitals that 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 emails to various healthcare provider professional societies. Additionally, the use of "alerts" embedded in electronic medical records of patients who underwent open-chest surgery and 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 United States 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 U.S. 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

Table X
Recommendations for *M. 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 (Thermofisher, formerly Trek Diagnostics, Cleveland, OH) use of Isolator tubes (Isolator 10, Oxoid; Isostatw System, WampoleTM). • Tissue mycobacterial cultures, broad range and mycobacterium-genus specific PCR and histopathological work up in case of re-operative heart surgery or surgery of distant foci.	I	C
Additional case finding tools • Review non-respiratory *M. avium* complex	IIb	C

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Table X (*continued*)

Recommendation	Class	Level
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

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

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 5—6 years; ii) Review of histopathology reports of culture negative cardiovascular infections with former CPB with the use of 3T-HCD within 5—6 years; iii) Review of sarcoidosis cases and former CPB with the use of 3T-HCD within 5—6 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 6 weeks to more than 5 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.

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

Table XI
Prevention of future *M. 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 [112]	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 [41,107]. Biofilm formation can be seen by discoloration/cloudiness in the fluid lines or circuits [112].	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-HCD 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 critical medical areas such as operating rooms [35,107]. Place HCD outside the OR, whenever possible. Encase HCD connected to the OR exhaust.	I	C
Testing of HCD			
NTM 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

Abbreviation: Operating room, OR; heater cooler device, HCD. CPB, cardiopulmonary bypass; ECDC, European Center of Disease Control.
Note:
[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 aerosolisation with other device types in limited investigations so far [28].

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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 [34,41,101—104]. 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 [36,104], 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 operating room (OR) [33,105—107] or ii) placing them in encasings with controlled air extraction via a duct to the theatre exhaust conduit (41). However, products such as 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 [106]. 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 [105,106,108]. 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 [33,108].

Institutions should continue to follow updated manufacturer instructions for cleaning and disinfection of these devices [109]. 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 program 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 MGIT medium had the highest sensitivity for *M. chimaera* detection in a recent study [111]. 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 can lead to the use of contaminated machines during this prolonged incubation period [106,111].

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 [112].

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 pediatric population are undefined [7,114]. Case finding strategies, device safety alerts and microbiological diagnostics need improvements [105]. Due to the rarity of the disease, the task force strongly encourages multicenter outcomes data collections to address key questions regarding optimal medical therapy, which is currently undefined. There are currently efforts to create a U.S. 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 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 requires clarification as well [7]. Collaborative discussions between medical device manufacturers, engineers and hospital epidemiology experts will be needed as new HCD 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 [46,112,116] as well as fungi, *Legionella* spp., non-fermenters like *Pseudomonas aeruginosa*, coagulase-negative staphylococci, *Micrococcus* spp. and Gram-positive rods can also colonize HCD [102] although the clinical relevance of colonization of the HCD with one or more of these organisms is unclear [46,116].

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Conflicts of interest statement

We declare no conflicts of interest. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors' contributions statement

BH, MH and PK wrote the first draft, and BH, JMM and BHo wrote the final version of the manuscript. All investigators contributed to review of papers, interpretation of the data, review of drafts and approval of the final guideline.

Appendix A

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