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Guidelines on *Mycobacterium chimaera*: an update

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ISCVID 2019 Lausanne; June 4, 2019

Growing need for international expertise on diagnosis, management and prevention of *M. chimaera* infections

Table 1. Published Cases of *Mycobacterium chimaera* Infection Related to the Heater–Cooler Unit

Outbreak Location/N/Citation	Latency		Mortality (%)
	Surgery to Symptoms	Symptoms to Diagnosis	
Europe/10/[7]	Median, 18 months	Median, 21 (5–40 months)	5/10 (50)
United Kingdom/30/[28]	Median, 14.5 months (range, 1.5–60 months)	Median, 7 weeks	18/30 (60)
Germany/5/[17]	Range, 5–60 months	NR	1/5 (20)
Pennsylvania/8/[26]	NR	Median, 1.2 years (1–27 months)	5/8 (63)
United States/24/[25]	NR	Mean, 1.6 years (range, 0.1–6.3 years)	11/24 (46)
New York/2/[31]	NR	Mean, 14.5 months (range, 12–17 months)	0
Montreal, Canada/2/[21]	Range, 13–16 months	Additional 2–3 months from presentation	0
Florida/1/[24]	72 months	NR	0
Minnesota/3/[22]	Range, 16–26 months	NR	2/3 (67)
Italy/1/[27]	14 months	12 months	0

Abbreviation: NR, not reported.

Relapse rate: 30 to 50%; **Mortality rates** 20-67%

Kasperbauer et al Clin Inf Dis 2019

Scope and aims

Aims

- Provide an update on *M. chimaera* epidemiology and risk factors
- Develop guidelines for diagnosis and management in individual patients
- Outline infection prevention and control recommendations.

Expert consensus of multidisciplinary group after review of available literature.

- Literature search since 2013, when the first two cases were published until March 2019.
- PubMed.gov database using the terms *Mycobacterium chimaera* or *M. chimaera* with the MESH terms "treatment", "cardiac", "HCD", "infection control" and specific antimicrobials and classes of antimicrobials. Only English language articles were included

Use of an **evidence-based scoring system** that was used in the European Society of Cardiology guidelines on infective endocarditis (1)

(1) Habib G et al EHJ 2015

Acknowledgements

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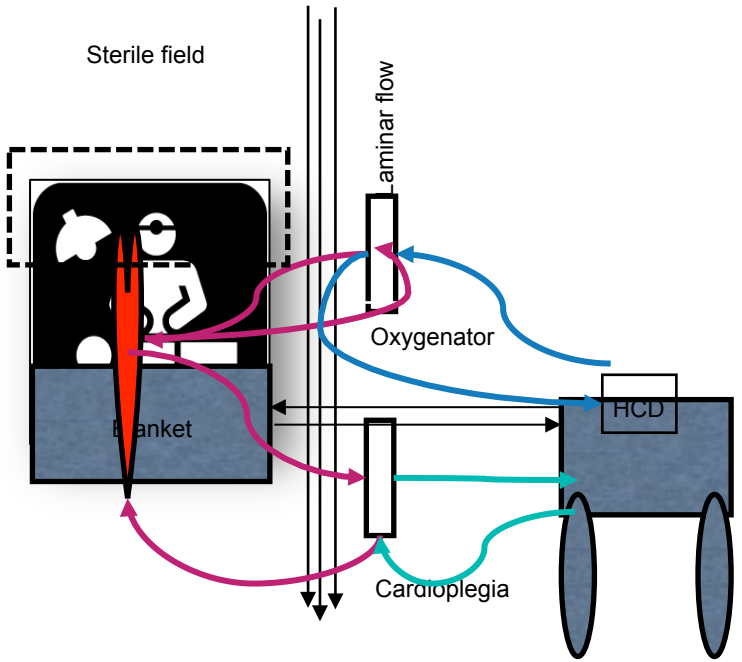
Endorsed by: Maximilian Halbe (Switzerland), Loreen Herwaldt (USA), Andreas Widmer (Switzerland), Volkmar Falk (Germany)

Source of outbreak: Heater Cooler Devices (HCD)

- **Key component of open cardiac procedures**
- HCUs have three water circuits to warm/ cool patients; the cardioplegia circuit or the cardiac bypass circuit

- Implicated devices (3T-HCD) widely distributed (70% market share). **Global outbreak with *M. chimaera***

- Further aspects:
  - **Mycobacterial biofilm formation in HCD**
  - **Laminar airflow management problem**

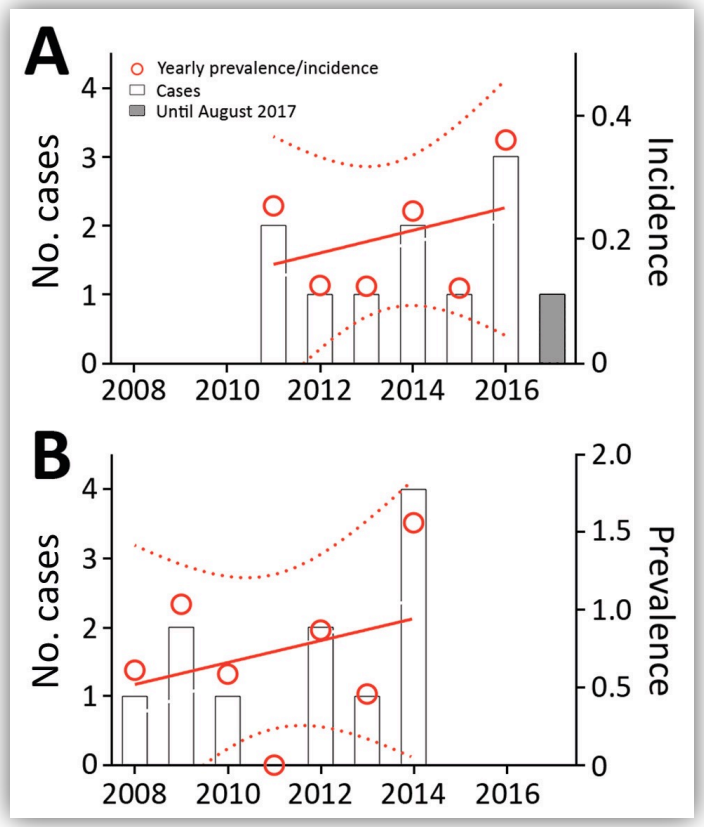


.Sax, Bloemberg, Hasse et al. Clin Infect Dis 2015; 61(1):67-75 [5]

Epidemiology

The absolute risk of acquiring *M. chimaera* infection is much lower than the risk of other types of infections after open chest surgery

- CH: 0.78 cases/1,000 procedures (95% CI 0.41-1.45)
- UK: 0.14 cases/1,000 procedures (95% CI 0.08-0.23)
- US: from 1/1,000 to 1/10,000



Sommerstein et al. Emerg Infect Dis. 2018;24(3):576-8; Chand et al Clin Infect Dis. 2016
Perkins et al MMWR Morb Mortal Wkly Rep. 2016;65(40):1117-8.

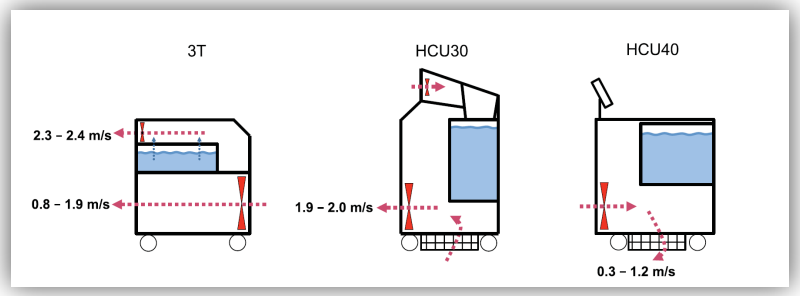
Risk factors

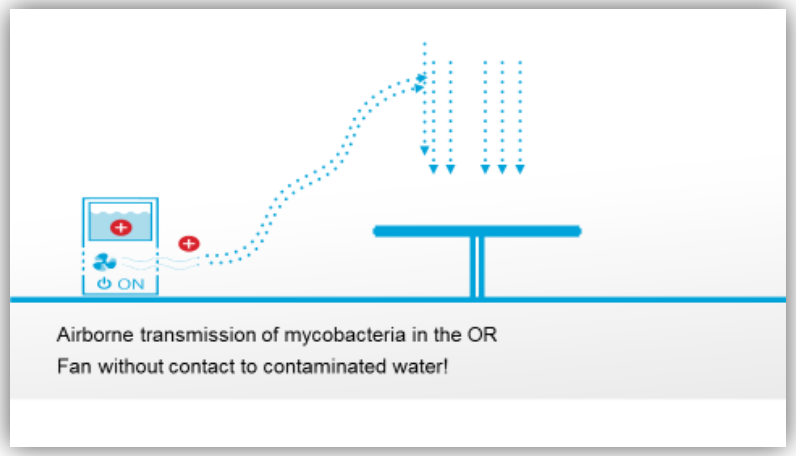
Cardiopulmonary bypass surgery
- Implantation of foreign material yes/no
- Length of extracorporeal circulation time

Heater cooler device (HCD)
- Type of HCD (Stockert 3T, Maquet, others)
- Contamination status with *Mycobacterium chimaera*
- Desinfection/ maintenance status

Operating room (OR)
- HCD in the OR or outside
- Distance of HCD from OR table
- Fan of HCD directs to OR table yes/no
- Laminar flow ventilation <u>insufficient</u>

Patient
- Immunosuppression yes/no





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Scriven et al Clin Microbiol Infect. 2018; Lyman et al Emerg Infect Dis. 2017;23(5):796-805; Sax et al Clin Inf Dis 2015;61(1):67-75; Kühl et al. Infect Control Hosp Epidemiol. 2018;39(7):834-40; Sommerstein et al Emerg Infect Dis. 2016;22(6):1008-13; Walker JT et al Lancet Infect Dis. 2017;17(10):1019; Stuckey M et al. 67th Annual Epidemic Intelligence Service Conference; April 17, 2018; Atlanta, GA. 2018

Population at risk for *Mycobacterium chimaera* infections

Procedure
Cardiopulmonary bypass surgery involving a 3T-HCD and one or more of the following:
• Prosthetic material used for cardiac valve or aorta repair
• Mechanical circulatory support device implantation
• Implant of palliative shunts, conduits or other prostheses for congenital heart disease
• Coronary artery bypass grafting
• Heart transplantation

Notes:
Aortic surgery highest risk; Coronary artery bypass grafting lowest risk
Infections have also been reported among patients following minimal-access cardiac surgery through small lateral thoracotomies

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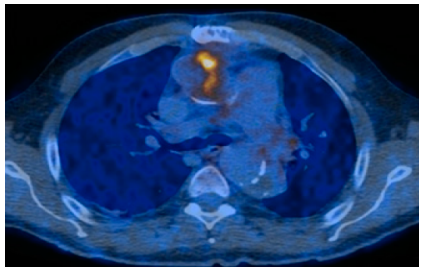
Kohler et al. Eur Heart J. 2015;36(40):2745-53; Scriven et al Clin Microbiol Infect. 2018; Lyman et al Emerg Infect Dis. 2017;23(5):796-805; Balsam et al J Card Surg. 2017;32(6):402-4; Hamad et al Ann Thorac Surg. 2017;104(1):e43-e5.; Cai et al Can J Anaesth. 2017;64(5): 513-6; Asadi et al J Thorac Cardiovasc Surg. 2017; Appenheimer A et al. Abstract 2391. ID Week 2016, New Orleans, LA, 29 October 2016

Clinics

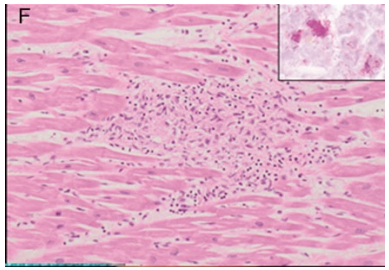
Diagnosis of endovascular *M. chimaera* infection can be difficult as initial symptoms may be non-specific, subtle and appear months to years after surgery

- Median latency. 15-17 months post-surgery (range from 6 weeks to as long as 6 years)
- Non-specific and indolent symptoms often prompt alternative diagnoses (eg sarcoidosis, FUO)
- Main clinical manifestations:

Endocarditis



Aortic graft infection



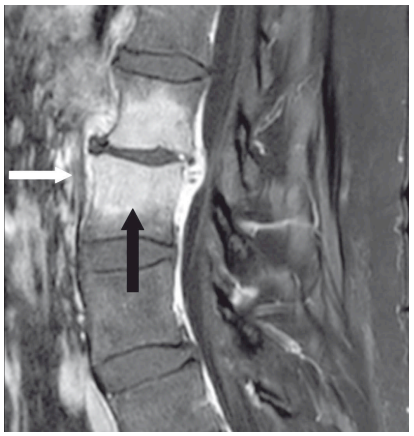
Mycocarditis

Sternotomy wound infection

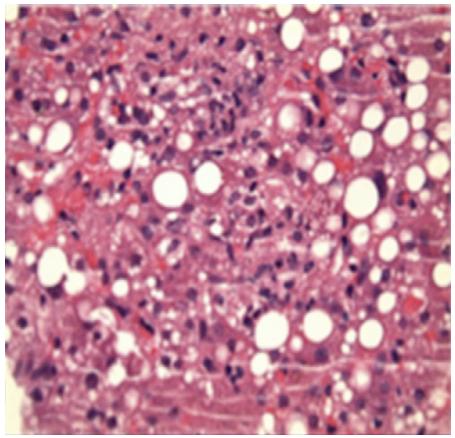
Kasperbauer et al. Clin Infect Dis 2019;68(7):1244-7; Kohler et al. Eur Heart J. 2015;36(40):2745-53; Scriven et al Clin Microbiol Infect. 2018;

Clinics – disseminated extrathoracic manifestations in panoply of organs

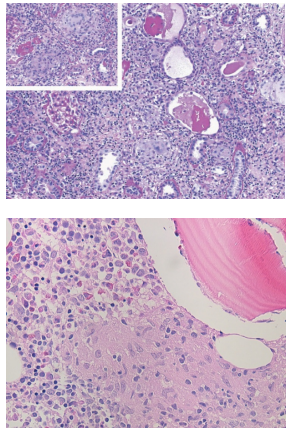
Extrathoracic symptoms may precede cardiac or vascular manifestations and signs of cardiac infection may be absent and detected only at surgery or post-mortem examination.



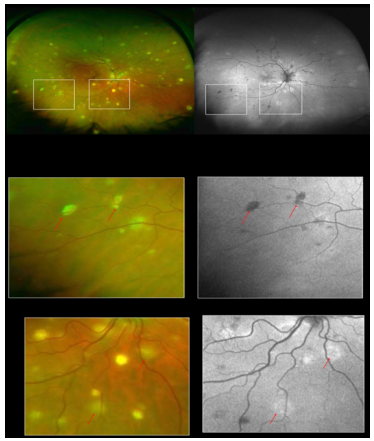
Osteoarticular manifestations



Cytopenia
Hemophagoctic syndrome



Nephritis
Hepatitis



Chorioretinitis
CNS involvement

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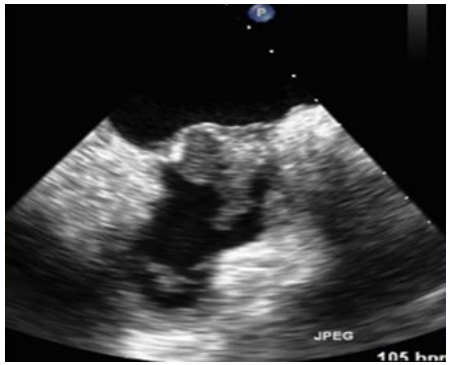
Kasperbauer et al. Clin Infect Dis 2019;68(7):1244-7; Kohler et al. Eur Heart J. 2015;36(40):2745-53; Scriven et al Clin Microbiol Infect. 2018; Chiesi et al. Infez Med. 2017;25(3):267-9; Gasch et al Rev Esp Cardiol (Engl Ed). 2018, Erb et al Swiss Medical Forum 2017;17(19):434–437; Zweifel et al Ophthalmology. 2016; Boni et al Retina. 2017

Imaging

Transesophageal echocardiogram (TOE)

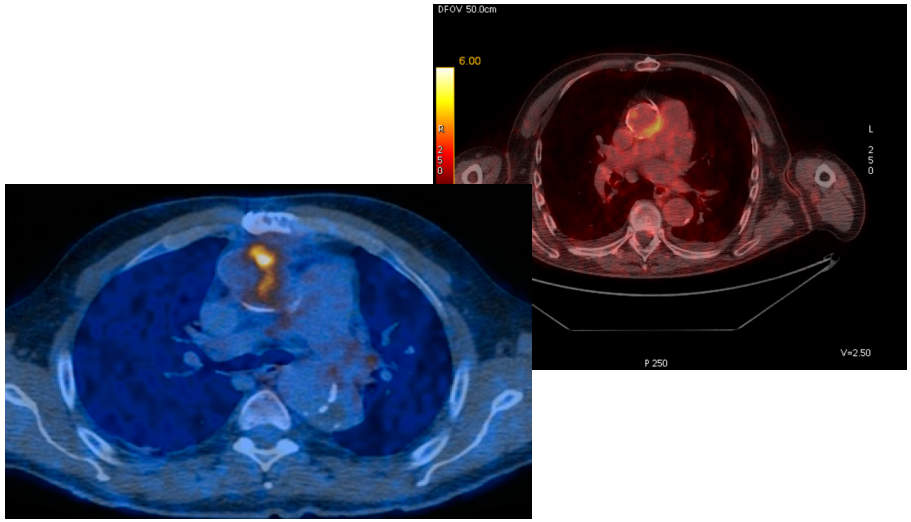
- Detection of cardiac vegetations
- aortic root collections
- Evaluation of valvular function



Sensitivity of TTE 33% compared to TOE (Scriven)

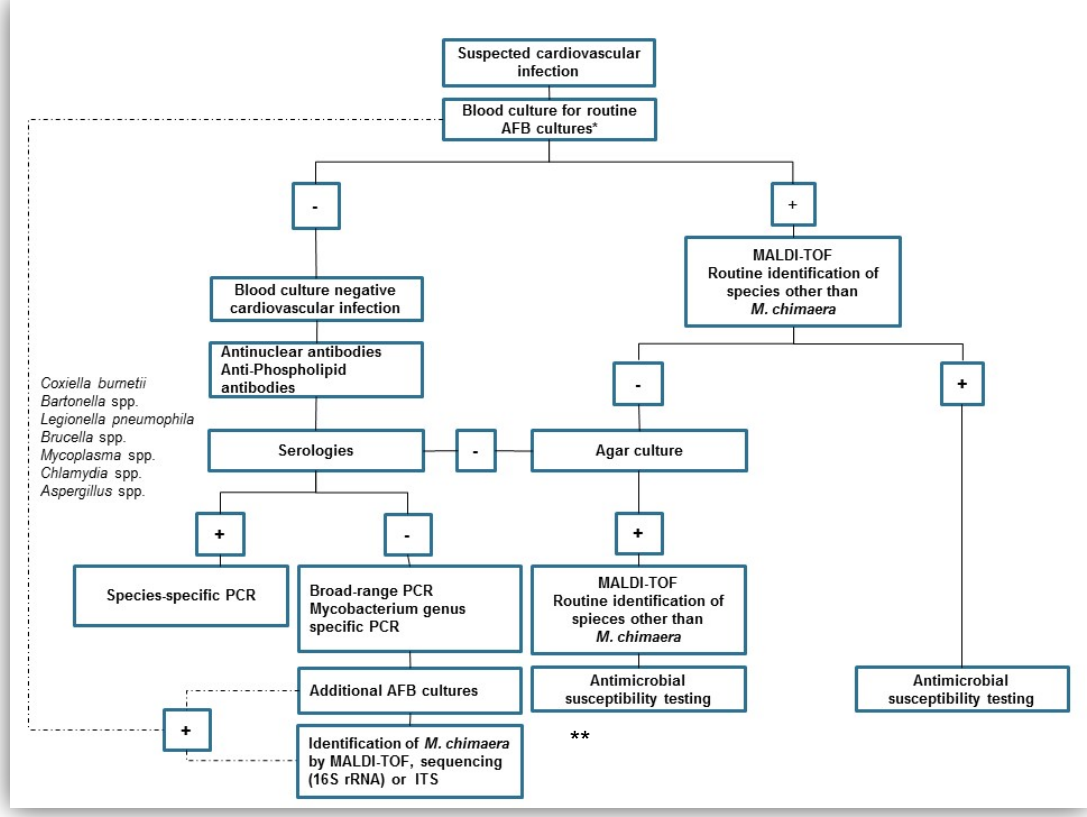
PET/CT imaging

- Aortic graft infection, Endocarditis with neg TOE
- Fever of unknown origin



Kohler Eur Heart Journal 2015; Sah et al. Eur J Vasc Endovasc Surg. 2015;49(4):455-64; Granadas et al. J Nucl Med 2016;57(11); 1726-32; Scriven J Clin Microbiol and Inf 2018.

Microbiological diagnosis



Positive cultures identified as MAC

- 16S rDNA (or *hsp65*) gene sequencing
- Sequencing of the ITS region
- MALDI-TOF (Bruker)

** Novel MALDI Biotyper Algorithm

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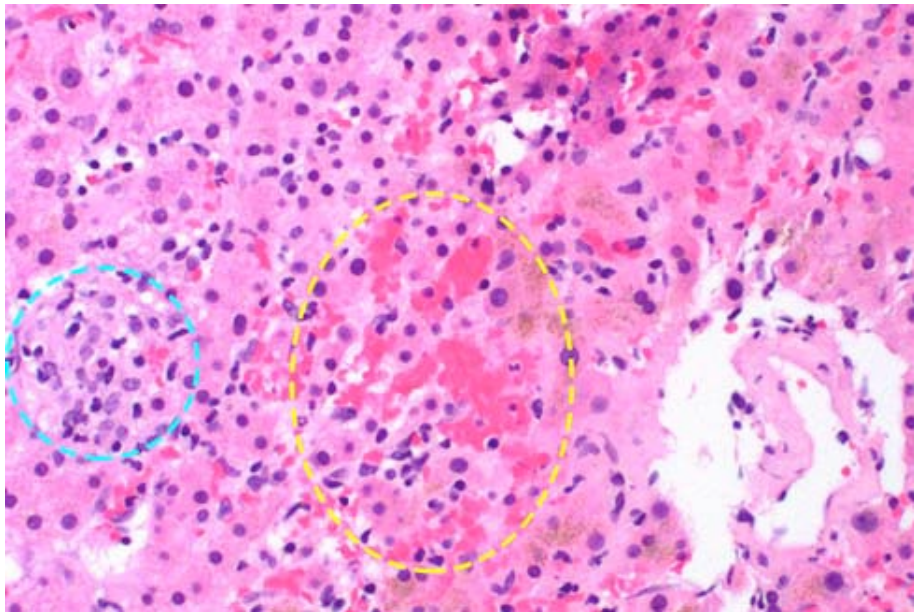
Adapted from Habib et al Eur Heart Journal 2015; Scriven et al Clin Microbiol and Infect 2018
Epperson Front Microbiol. 2018;9:3140; Tortoli et al Int J Syst Evol Microbiol. 2004;54(Pt 4):1277-85

Histopathology

- Resected cardiac valve or other infected tissue and embolic fragments should be examined for possible mycobacterial infection
- The **detection of non-caseating granulomas and foamy swollen macrophages with/without AFB** is consistent with NTM infection, including those due to *M. chimaera* in the appropriate clinical setting
- **Mycobacterium genus-specific PCR** should be considered if histopathology is indicative for NTM



Characteristic dual centrilobular pattern of injury:
- Sinusoidal histiocytes (blue circle)
- Sinusoidal venous obstructive like changes (yellow circle).

Shafizadeh N et al. Am J Surg Pathol. 2019;43(2):244-50.
Deggim-Messmer et al EBioMedicine. 2016;9:228-37
Marchetti G et al. J Clin Microbiol. 1998;36(6):1512-7

Treatment regimens of endovascular *Mycobacterium chimaera* infection

Type of *Mycobacterium chimaera* strain	Suggested regimen
Wild-type *Mycobacterium chimaera*	
• First line therapy	Azithromycin, rifampin/(rifabutin), ethambutol, amikacin
• Second line therapy	Clarithromycin, rifabutin/(rifampin), ethambutol, amikacin
Drug-resistant *Mycobacterium chimaera**	Consider repeat testing to confirm resistances to macrolide and/or amikacin are rare.

*Clinicians have used clofazimine, bedaquiline, moxifloxacin or linezolid in certain instances.

Redo surgery – associated with lower mortality rates

	Total patients		Death *		Ongoing therapy		Cure**		Relapse	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Antimicrobial therapy and removal of implant material	46	(100)	14	(30)	24	(52)	8	(17)	3	(6.5)
Antimicrobial therapy without removal of implant material	51	(100)	30	(59)	21	(41)	3	(5.8)	2	(3.9)
Overall	97	(100)	44	(45)	45	(36)	11	(11)	4	(4.1)

*Chi-square test: P=0.008; ** Chi-square test: P=0.14

- Valve replacement surgery associated with better outcomes.
- Conservatively managed patients with anti-mycobacterial treatment often experience break through infections or relapse.

Kohler et al.Eur Heart J. 2015 Oct 21;36(40):2745-53; Scriven J J Clin Microbiol Inf 2018; Cai et al Can J Anaesth. 2017 May;64(5):513-6 ; Tan et al Open Forum Infect Dis. 2016 Sep;3(3):ofw131; Appenheimer A. (Abstract 2391). ID Week 2016, New Orleans, LA, 29 October 2016; Boni et al Retina. 2017; Hamad et al Ann Thorac Surg. 2017 Jul;104(1):e43-e5; Asadi et al J Thorac Cardiovasc Surgery. 2017; Balsam et al J Card Surg. 2017 Jun;32(6):402-4; Chiesi et al Infez Med. 2017 Sep 1;25(3):267-9; Overton et al Intern Med J. 2018 Dec;48(12):1514-20; Shafizadeh et al. Am J Surg Pathol. 2019 Feb;43(2):244-50; Cappabianca et al J Cardiovasc Med (Hagerstown). 2018 Dec;19(12):748-55; Rudikoff AG et al J Cardiothorac Vasc Anesth. 2018 Sep 11; Shah VN et al Ann Thorac Surg. 2019 Feb;107(2):e89-e91; O' Neill CR et al. Open Forum Infect Dis. 2018 Feb;5(2):ofy018.

Future research

Many aspects of diagnosis, management, and prevention that need further research

- Risk of involvement of the **pediatric population** are undefined.
- Due to the rarity of the disease, **multicenter outcomes data collections** needed to address key questions regarding epidemiology, clinical manifestations, treatment, and outcomes for patients with related infections (Link: www.NTMInfect.org)
- **New HCD design**
- **Reliable decontamination and identification of agents that can disrupt biofilms** and increase chlorine susceptibility of mycobacteria are required.
- **Role of other mycobacteria as well as fungi, *Legionella* spp., non-fermenters like *Pseudomonas aeruginosa* in HCDs.**


Questions?
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European Heart Journal
doi:10.1093/eurheartj/ehv342

FASTTRACK CLINICAL RESEARCH
Cardiovascular surgery

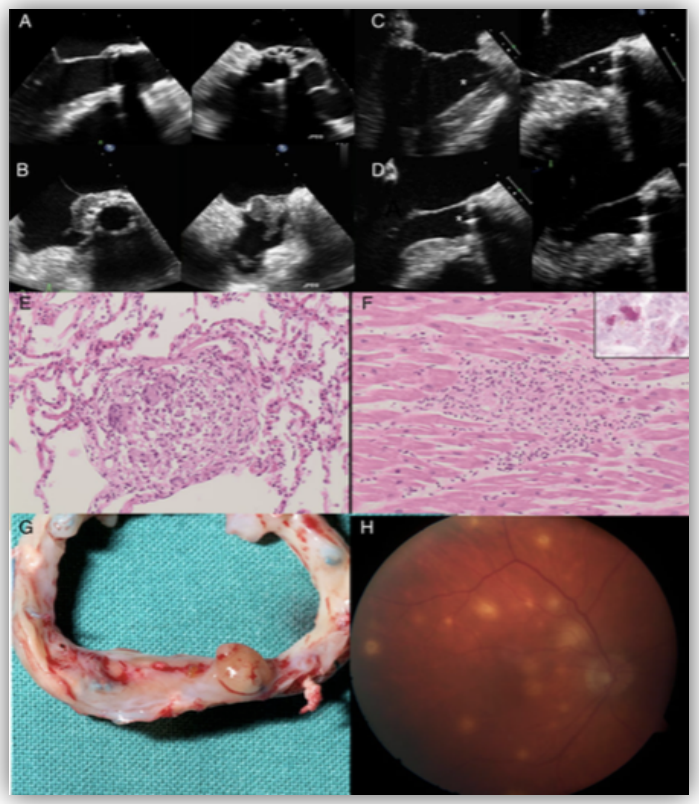
Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery

Philipp Kohler[1], Stefan P. Kuster[1], Guido Bloemberg[2], Bettina Schulthess[2,3], Michelle Frank[4], Felix C. Tanner[4], Matthias Rössle[5], Christian Böni[6], Volkmar Falk[7,8], Markus J. Wilhelm[7], Rami Sommerstein[1], Yvonne Achermann[1], Jaap ten Oever[9], Sylvia B. Debast[10], Maurice J.H.M. Wolfhagen[10], George. J. Brandon Bravo Bruinsma[11], Margreet C. Vos[12], Ad Bogers[13], Annerose Serr[14], Friedhelm Beyersdorf[15], Hugo Sax[1], Erik C. Böttger[2,3], Rainer Weber[1], Jakko van Ingen[16†], Dirk Wagner[17†], and Barbara Hasse[1†*]

New disease entity with high mortality rate

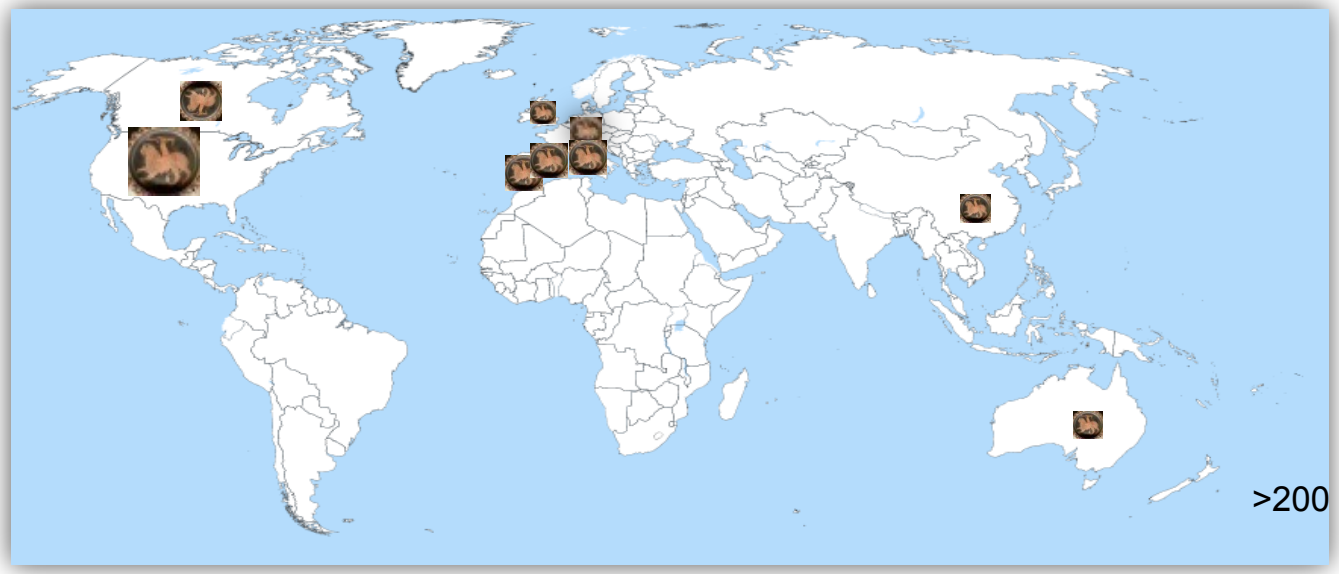
(8/10 patients dead by now)

- Long delays since cardiac surgery and symptom onset
- Need of directed microbiologic testing
- 8/10 surgical re-intervention despite anti-mycobacterial therapy
- Many break-through infections



Kohler et al. Eur Heart J. 2015;36(40):2745-53

We expect to see more cases in the future…



>200 cases worldwide

Medical Device Reporting: 86 patients
339 MDR reports (99 facilities, 5 HCD manufacturers)

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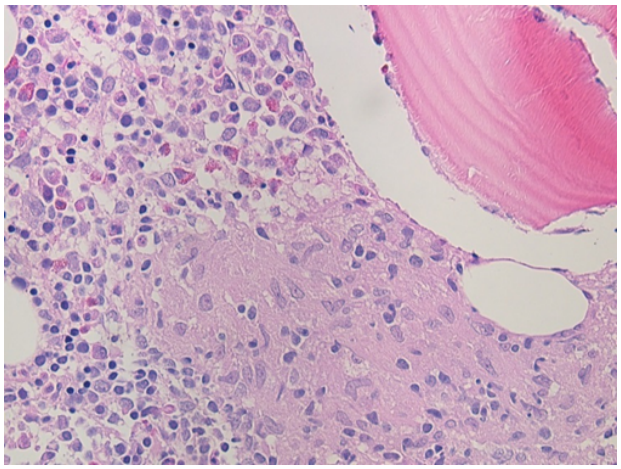
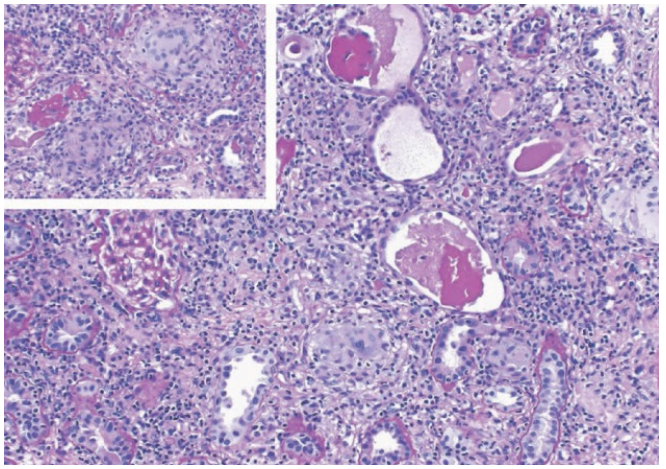
Allen KB et al. Ann Thorac Surg. 2017 Oct;104(4):1237-1242
Kasperbauer et al. Clin Infect Dis 2019;68(7):1244-7

Immune reconstitution inflammatory syndrome

In cases 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
- Bone





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Brown CS BMC Infect Dis. 2016;16:479; Phiilips P et al Clin Inf Dis 2005; 41(10):1483-97. Kohler et al. European Heart Journal 2015; Hasse B et al, ECCMID 2017, Erb et al Swiss Medical Foum 2017

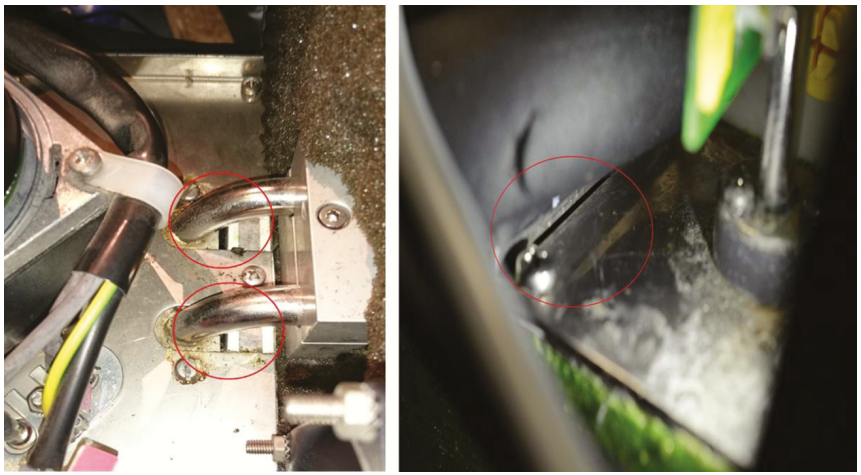
Patient notification/ investigation and provider notification

Recommendation
Patient notification should be considered**.**
Provider notification should be considered and has been successful in case detection**.**
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

Identification and prevention of *M. chimaera* exposure

Guidelines for all HCDs

- Register HCD, patient and date of use
- **Use sterile all bacteria filtered water including for ice**
- **Cleaning and disinfection** measures to manufacturer
- **Separate HCD exhaust air from OR**.



Protocol for case detection, laboratory diagnosis and environmental testing of *M. chimaera* infections potentially associated with heater-cooler units by ECDC
Link: http://ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/about_programme.aspxEU

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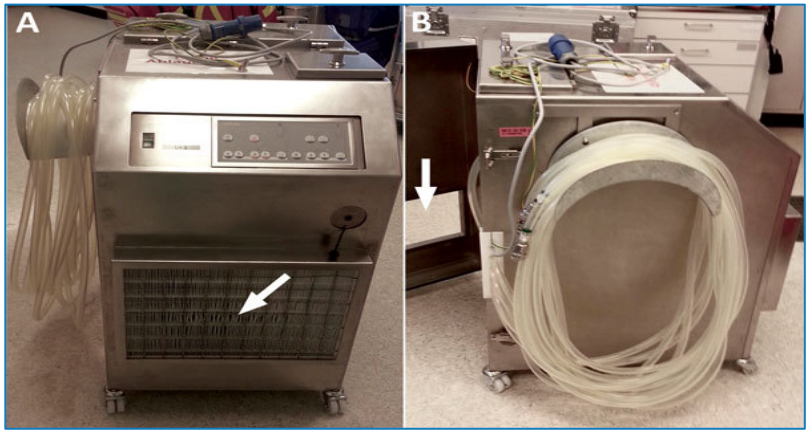
Schreiber et al. Emerg Infect Dis. 2016;22(10):1830-3; Marra et al Clin Infect Dis. 2017;65(4):669-74.
Lyman et al Emerg Infect Dis 2017;23(5):796-805;
Sommerstein et al Infect Control Hosp Epidemiol. 2016:1-6

Identification and prevention of *M. chimaera* exposure

Guidelines for hospitals with 3T-HCDs

- Strict separation between air in the OR and the potentially contaminated air around HCD.
- Place HCD outside the OR, whenever possible.
- Implementation of the vacuum seal device on existing 3T-HCD is recommended
- All 3T-HCD manufactured should ideally be removed from service



- Encase HCD connected to the OR exhaust.

Schreiber et al. Emerg Infect Dis. 2016;22(10):1830-3; Marra et al Clin Infect Dis. 2017;65(4):669-74.
Lyman et al Emerg Infect Dis 2017;23(5):796-805;
Sommerstein et al Infect Control Hosp Epidemiol. 2016:1-6

*LivaNova https://investor.livanova.com/static-files/9cf37b42-8164-4eff-9820-7504e5dc3c1f

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing of *M. chimaera* isolates should be performed by experienced reference laboratories

***M. chimaera* isolates should be saved for future testing** if no baseline AST has been performed

Clarithromycin and amikacin MIC testing is recommended

No routine testing of other antimicrobial substances (rifampin, rifabutin, ethambutol and streptomycin)

Breakpoints for antimicrobials used in the treatment of NTM infections were re-defined in the CLSI M24Ed3 and M62Ed1 documents.