The nightmare of *Mycobacterium chimaera*

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No relevant disclosures or COI
Background

“…a thing of immortal make, not human, lion-fronted and snake behind, a goat in the middle”

Homer; Iliad 6 179-182
**Mycobacterium chimaera**

Slowly growing non-tuberculous mycobacterium (NTM)
MAC-A 16s-23S ITS sequevar

«Virulence greater than other MAC organisms»

Environmental sources (water, soil)

### Six heart surgery patients with disseminated *M. chimaera* infections in one hospital

All patients had cardiac implants

Latency 1.7-3.6 years

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#### Table: Prolonged Outbreak of Mycobacterium chimaera Infection After Open-Chest Heart Surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of Index Surgery</th>
<th>Latency, y</th>
<th>Heart Surgery Implant</th>
<th>Material</th>
<th>Manifestations</th>
<th>Positive Cultures for <em>Mycobacterium chimaera</em></th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>58 Aug 2008</td>
<td>2.9</td>
<td>Minimally invasive reconstruction</td>
<td>25-mm Dacron arterial conduit (model 4402, series no. 171202, lot no. 061/13)</td>
<td>Layers of Dacron arterial conduit covered by polyethylene</td>
<td>Endocarditis, pericarditis, pericardial effusion</td>
<td>Blood, cardiac tissue, pleural effusion, septum</td>
</tr>
<tr>
<td>Patient 2</td>
<td>May 2009</td>
<td>1.5</td>
<td>Composite graft for aortic arch</td>
<td>25-mm ATS composite graft (model 54401W, series no. 191202, lot no. 101/23A)</td>
<td>Heart valve prosthesis Goretex double woven dacron</td>
<td>Endocarditis, pericarditis, pericardial effusion</td>
<td>Blood, aorta, bone marrow, valvular</td>
</tr>
<tr>
<td>Patient 3</td>
<td>June 2009</td>
<td>3.5</td>
<td>Native valve reconstruction</td>
<td>32-mm Dacron aortic root replacement graft (model 4402, series no. 936502, lot no. 005/02)</td>
<td>Layers of Dacron aortic root replacement graft covered by polyethylene</td>
<td>Endocarditis, endocarditis, pericarditis, pericardial effusion</td>
<td>Cardiac tissue and pericardium, bone marrow</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Oct 2009</td>
<td>3.4</td>
<td>Aortic valve replacement</td>
<td>29-mm ATS Open Port AP Series Heart Valve (model 534324, series no. 438713)</td>
<td>Heart valve prosthesis Goretex double woven dacron</td>
<td>Endocarditis, endocarditis, pericarditis, pericardial effusion</td>
<td>Cardiac tissue and pericardium, bone marrow</td>
</tr>
<tr>
<td>Patient 5</td>
<td>May 2012</td>
<td>1.7</td>
<td>Aortic root and arch replacement</td>
<td>ATS Aortic Root B32285, series no. 532100</td>
<td>Valve prosthesis Goretex double woven dacron</td>
<td>Endocarditis, endocarditis, pericarditis, pericardial effusion</td>
<td>Venous bone, Granulomatous endocarditis</td>
</tr>
<tr>
<td>Patient 6</td>
<td>March 2012</td>
<td>1.8</td>
<td>Aortic root and arch replacement</td>
<td>Metallic-FreeStyle Aortic Valve (model 723, series no. 220-002, lot no. 0364, series no. 00011550301, lot no. 000448-1001)</td>
<td>Valve prosthesis Goretex double woven dacron</td>
<td>Venous bone, Granulomatous endocarditis</td>
<td>Venous bone, Granulomatous endocarditis</td>
</tr>
</tbody>
</table>
Outbreak investigation

Observations
Video analysis
Interviews
Workflow analysis
Mycobacteria cultures water/air samples

Patient heating blanket water circuit
Heater-cooler device water tanks/circuits
Operating room air
Showers
Drinking water fountains

© by author
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
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)

An imaginary clinical case

63 year old male with aortic surgery 2013. Presents in 2019 with fever on unknown origin

Laboratory
- Elevated CRP, ESR, transaminases, bicytopenia
- Blood cultures so far negative

Imaging
- TOE not indicative of infection
- PET/CT with increased metabolic activity at the prosthetic aortic valve

Epidemiology

Risk factors
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 1/1000 to 1/10,000

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 **insufficient**

Patient
• Immunosuppression yes/no

### Population at risk for *Mycobacterium chimaera* infections

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

**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

Diagnosis

- Clinical picture
- Imaging
- Microbiology
- Histopathology
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 (e.g., sarcoidosis, FUO)
- Main clinical manifestations:

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
Hemophagocytic syndrome

Nephritis
Hepatitis

Chorioretinitis
CNS involvement

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

Imaging

Transesophageal echocardiogram (TOE)
- Detection of cardiac vegetations
- Aortic root collections
- Evaluation of valvular function

PET/CT imaging
- Aortic graft infection, Endocarditis with neg TOE
- Fever of unknown origin

Sensitivity of TTE 33% compared to TOE (Scriven)

An imaginary clinical case would be a perfect match!

63 year old male
Aortic surgery 2013, FUO 2019 → Latency 6 years

Laboratory
• Elevated CRP, ESR, transaminases, bicytopenia
• Blood cultures negative

Imaging
• TOE not indicative of infection
• PET/CT with increased metabolic activity at the prosthetic aortic valve

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

Microbiological diagnosis

- **Mycobacterial cultures** from invasive sample
- **Mycobacterial blood cultures**
  - BACTEC Myco Lytic/F bottles, BD, Franklin Lakes, NJ, USA
  - VersaTrek (ThermoFisher, Cleveland, OH)
- **Mycobacterium genus-specific PCR** from invasive sample
- **NGS test** in plasma (KARIUS, Redwood City, USA)

Diagnostic sensitivity of a single heparin blood collection tube 68%.

Scriven et al Clin Microbiol and Infect 2018
Epperson Front Microbiol. 2018;9:3140
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).

Treatment

- Medical treatment
- Surgical treatment
Multidisciplinary hospital patient management

Management of *M. chimaera*-infected patients by a multidisciplinary ‘Endocarditis Team’ needed.

A patient may present initially to a variety of medical specialties.

Once infection is diagnosed, expertise from various medical specialties is needed.
Treatment regimens of endovascular *Mycobacterium chimaera* infection

<table>
<thead>
<tr>
<th>Type of <em>Mycobacterium chimaera</em> strain</th>
<th>Suggested regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type <em>Mycobacterium chimaera</em></td>
<td></td>
</tr>
<tr>
<td>• First line therapy</td>
<td>Azithromycin, rifampin/(rifabutin), ethambutol, amikacin*</td>
</tr>
<tr>
<td>• Second line therapy</td>
<td>Clarithromycin, rifabutin/(rifampin), ethambutol, amikacin*</td>
</tr>
<tr>
<td>Drug-resistant <em>Mycobacterium chimaera</em>*</td>
<td>Consider repeat testing to confirm resistance since resistance to macrolides and/or amikacin are rare.</td>
</tr>
</tbody>
</table>

*Other drugs such as clofazimine, bedaquiline, moxifloxacin or linezolid were used by clinicians.
Adverse drug reactions and treatment monitoring

Monitoring of vestibular function and audiograms
• Monthly in patients receiving intravenous amikacin; periodically in patients receiving macrolides

Periodic ophthalmologic examinations with visual acuity, red-green color discrimination, confrontation visual field testing and dilated fundus examination
• Ethambutol, linezolid and/or rifabutin

Therapeutic drug monitoring (TDM)
• Amikacin; ethambutol in case of renal insufficiency
• Macrolide blood levels in case of rifampin combination therapy
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.
Redo surgery – lower mortality rates

• **Revision surgery** with removal of all cardiovascular prosthetic material even if a cardiac valve/vascular graft is functioning well

• **Sternal surgical site infections:** extensive debridement with removal of sternal metal wires

• **Source control should include all extracardiac foci**

• Optimal timing of surgery unknown.

*M. chimaera* mediastinitis/ aortic graft infection with sites of dissemination

Decisive factor: mycobacterial biofilm formation

Aortic graft infection
- 118 days treatment
- Culture positive!

Culture results positive in the bulk of patients, regardless of whether or not anti-mycobacterial therapy has been previously administered.

Courtesy to Annette Moter, Stefan Erb, Nina Khanna et al.
Redo surgery – associated with lower mortality rates

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Death *</th>
<th>Ongoing therapy</th>
<th>Cure**</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial therapy and removal of implant material</td>
<td>46 (100)</td>
<td>14 (30)</td>
<td>24 (52)</td>
<td>8 (17)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Antimicrobial therapy without removal of implant material</td>
<td>51 (100)</td>
<td>30 (59)</td>
<td>21 (41)</td>
<td>3 (5.8)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Overall</td>
<td>97 (100)</td>
<td>44 (45)</td>
<td>45 (36)</td>
<td>11 (11)</td>
<td>4 (4.1)</td>
</tr>
</tbody>
</table>

*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 breakthrough infections or relapse.

Follow up and prognosis

<table>
<thead>
<tr>
<th>Outbreak Location/Note</th>
<th>Surgery to Symptoms</th>
<th>Symptoms to Diagnosis</th>
<th>Latency</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe/10(17)</td>
<td>Median, 18 months</td>
<td>Median, 21 (5–42 months)</td>
<td>NR</td>
<td>9/10 (90%)</td>
</tr>
<tr>
<td>United Kingdom/6(10)</td>
<td>Median, 14.5 months (range, 1.5–30 months)</td>
<td>Median, 7 weeks</td>
<td>13/30 (43%)</td>
<td></td>
</tr>
<tr>
<td>Germany/5/17</td>
<td>Range, 5–60 months</td>
<td>NR</td>
<td>1/5 (20%)</td>
<td></td>
</tr>
<tr>
<td>Pennsylvania/1/125</td>
<td>NR</td>
<td>Median, 1.2 years (1–27 months)</td>
<td>5/10 (50%)</td>
<td></td>
</tr>
<tr>
<td>United States/24/25</td>
<td>NR</td>
<td>Mean, 1.6 years (range, 0.1–6.3 years)</td>
<td>11/24 (46%)</td>
<td></td>
</tr>
<tr>
<td>New York/2/31</td>
<td>NR</td>
<td>Mean, 14.5 months (range, 12–17 months)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Montreal, Canada/2/32</td>
<td>Range, 13–16 months</td>
<td>Additional 2–3 months from presentation</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>France/1/124</td>
<td>22 months</td>
<td>NR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Minnesota/1/126</td>
<td>Range, 16–26 months</td>
<td>NR</td>
<td>2/3 (67%)</td>
<td></td>
</tr>
<tr>
<td>Italy/1/127</td>
<td>14 months</td>
<td>12 months</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NR=not reported.

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

Factors associated with treatment failure:
- 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
Infection control
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


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.


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

- Future research
- Case registry
- Multidisciplinary guidelines
Future research /Case registry

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

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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
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