Global *Mycobacterium chimaera* Outbreak in Cardiac Surgery

Hugo Sax and Barbara Hasse, University of Zurich Hospital

Sponsored by the World Health Organization

Global *Mycobacterium chimaera* outbreak in cardiac surgery

Hugo Sax, MD
Barbara Hasse, MD

Division of Infectious Diseases and Hospital Epidemiology
University Hospital of Zurich
University of Zurich
Zurich, Switzerland

Hosted by Julie Storr
World Health Organization, Geneva

Prosthetic valve endocarditis mitral valve

**Case #1 | 58-year-old male**

2008 Mitral annuloplasty ring

2010 Dx of systemic sarcoidosis

2011 Respiratory distress, severe mitral and aortic valve insufficiency, at surgery fraying of ring and valve destruction...
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Fever of unknown origin and composite graft infection

**Case #2 | 58-year-old male**

2010 Composite (aortic valve & arch) graft for aortic dissection

2011 Fever of unknown origin, splenomegaly, renal insufficiency, liver enzyme, pancytopenia. *M. chimaera* cultured from bone marrow, blood cultures, urine, tracheal swab.

2012 Exodus due to splenic rupture

---

*Mycobacterium chimaera*: what is known

Microbiology
Slow growing non-tuberculous mycobacterium

Acid-fast, non-motile and non-spore forming coccobacilli

Formerly classified as *Mycobacterium intracellulare*, described by Tortoli 2004

Clinics
Lung disease among immunocompromised/elderly patients
Assumed as «less virulent…..”

Environment
Not found in water systems in Europe, but the US

---


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Really «less virulent»….?

Operated two years apart at the same hospital with a rare pathogen

Cluster

Two or more cases of a relatively uncommon event or disease related in time and/or place perceived to be greater than expected by chance.

Outbreak

The occurrence in a community or region of cases of an illness with a frequency clearly in excess of normal expectancy.

The number of cases indicating presence of an outbreak will vary according to the infectious agent, size and type of population exposed, previous experience or lack of exposure to the disease and time and place of occurrence.

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Randomly amplified polymorphic DNA
(primers according *M. abscesses*)

No other matching strains found in hospital

FIG 2. *Mycobacterium chimaera* strain typing using randomly amplified polymorphic DNA (RAPD)-PCR. Shown are RAPD-PCR patterns of *M. chimaera* clinical isolates from the two patients (lane 1, patient 1; lane 2, patient 2) and of eight respiratory culture isolates from eight different patients (lanes 3 to 10). RAPD-PCR patterns were generated with primers IS986-EP (A) and OPA18 (B). MW, molecular weight marker.

Outbreak investigation


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<table>
<thead>
<tr>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Video analysis</td>
</tr>
<tr>
<td>Interviews</td>
</tr>
<tr>
<td>Workflow analysis</td>
</tr>
<tr>
<td>Mycobacteria cultures</td>
</tr>
</tbody>
</table>

- Patient heating blanket water circuit
- Heater-cooler unit water tanks/circuits
- Showers
- Drinking water fountains
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Heart-Lung-machine
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Heat-exchangers

Cardioplegia solution  Patient blood circuit

Sorin Stockert T3

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Air cultures with heater-cooler unit turned on

Air cultures with heater-cooler unit turned off

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Air cultures with heater-cooler unit turned on

Air cultures with heater-cooler unit turned off

WATER SYSTEM

Operating rooms

Intensive care unit

Ward

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---

**Many outbreaks of surgical site infections with NTM**

<table>
<thead>
<tr>
<th>Report</th>
<th>Location</th>
<th>Year</th>
<th>Type of Treatment</th>
<th>Report in</th>
<th>Region</th>
<th>Surgical Site Infection (SSIs)</th>
<th>Number of Infections (n)</th>
<th>Etiology</th>
<th>Typing Method</th>
<th>Clustering</th>
<th>Source</th>
<th>Source of Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch</td>
<td>Cardiology</td>
<td>2016</td>
<td>Cardiac surgery</td>
<td>Not specified</td>
<td>Amsterdam</td>
<td><em>Mycobacterium chimaera</em></td>
<td>2</td>
<td>DNA fingerprinting</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>Cardiology</td>
<td>2017</td>
<td>Cardiac surgery</td>
<td>Not specified</td>
<td>Tokyo</td>
<td><em>Mycobacterium kansasii</em></td>
<td>4</td>
<td>DNA fingerprinting</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
<td></td>
</tr>
<tr>
<td>Scottish</td>
<td>Cardiology</td>
<td>2018</td>
<td>Cardiac surgery</td>
<td>Not specified</td>
<td>Edinburgh</td>
<td><em>Mycobacterium fortuitum</em></td>
<td>3</td>
<td>DNA fingerprinting</td>
<td>Not identified</td>
<td>Not identified</td>
<td>Not identified</td>
<td></td>
</tr>
</tbody>
</table>

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More cases

Mitral ring endocarditis

**Case #3 | 61-year-old male**
- 2009 Mitral valve reconstruction
- 2012 Arthritis due to *M. chimaera*
- 2013 Mitral ring endocarditis
- 2014 Redo surgery

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Aortic prosthetic valve endocarditis

**Case #4 | 49-year-old male with Crohn’s disease**

- Treatment with azathioprin
- 2009 Aortic valve replacement
- 2013 Progressive Dyspnea, Ascites, icterus

Prosthetic valve endocarditis
Redo surgery

Composite graft infection

**Case #5 | 59-year-old male**

- 2010 Composite graft replacement
- 2013 Spondylodiscitis
- 2014 Composite graft infection due to *M. chimaera*
- 2014 Redo surgery

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Aortic arch infection

**Case #5 | 60-year-old male**
2010 Aortic arch replacement
2014 Aortic graft infection due to *M. chimaera*
2014 Debridement of periaortic tissue, retention of graft

Grade 5, focal and intense FDG-uptake plus fluid collections/abscess formation

---

Time line of infections

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### Prostheses differed in materials and manufacturers

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Date of index surgery</th>
<th>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>1</td>
<td>58</td>
<td>13.08.2014</td>
<td>10/687</td>
<td>Metal valve reconstruction</td>
<td>Layers of filigree blooming ring with layers of polymer and fat tissue</td>
<td>Endocarditis, pericarditis, myocarditis, mediastinitis, pericardial effusion</td>
<td>Grossly normal hepatitis, peritoneum</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>25.01.2014</td>
<td>10/687</td>
<td>Composite graft for aortic reconstruction</td>
<td>Layers of filigree blooming ring with layers of polymer and fat tissue</td>
<td>Endocarditis, pericarditis, myocarditis, mediastinitis, pericardial effusion</td>
<td>Grossly normal hepatitis, peritoneum</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>12.06.2014</td>
<td>10/687</td>
<td>Metal valve reconstruction</td>
<td>Layers of filigree blooming ring with layers of polymer and fat tissue</td>
<td>Endocarditis, pericarditis, myocarditis, mediastinitis, pericardial effusion</td>
<td>Grossly normal hepatitis, peritoneum</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>31.05.2014</td>
<td>10/687</td>
<td>Aortic valve replacement</td>
<td>Heart valve prosthesis: metallic, sutured, polyurethane, fibrous, non-fibrous, non-fibrous</td>
<td>Grossly normal hepatitis, peritoneum</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>30.07.2014</td>
<td>10/687</td>
<td>Aortic root and valve replacement</td>
<td>Heart valve prosthesis: metallic, sutured, polyurethane, fibrous, non-fibrous, non-fibrous</td>
<td>Grossly normal hepatitis, peritoneum</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>25.02.2014</td>
<td>10/687</td>
<td>Aortic root and valve replacement</td>
<td>Heart valve prosthesis: metallic, sutured, polyurethane, fibrous, non-fibrous, non-fibrous</td>
<td>Grossly normal hepatitis, peritoneum</td>
<td></td>
</tr>
</tbody>
</table>

6 infected patients 3000 open-chest heart surgery interventions

---

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Switzerland investigation in 2014

16 cardiac surgery centres

8 grew *M. chimaera* from heater-cooler units

No further patient at that time

Going public

July 14, 2014

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---

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


---

10 patients (CH, D, NL)

1-4 y latency since cardiac surgery

Peripheral or systemic manifestations

8/10 surgical re-intervention despite Rx

6/10 break-through infections, 4 fatal

3 patients are being monitored post-Rx

---

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To our best knowledge

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland</td>
<td>7 patients</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4 patients</td>
</tr>
<tr>
<td>Germany</td>
<td>5 patients</td>
</tr>
<tr>
<td>UK</td>
<td>20 patients</td>
</tr>
<tr>
<td>Spain</td>
<td>1 patient</td>
</tr>
<tr>
<td>US</td>
<td>11 patients</td>
</tr>
<tr>
<td>France</td>
<td>2 patients</td>
</tr>
<tr>
<td>Irland</td>
<td>2 patients</td>
</tr>
</tbody>
</table>

And counting…
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Now the work starts for clinicians…

Invasive *M. chimaera* infections

---

**Table 3  Recommendations for future case detection**

<table>
<thead>
<tr>
<th>Exposure criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A patient having undergone surgery requiring cardiopulmonary bypass prior to symptoms of infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valve endocarditis</td>
</tr>
<tr>
<td>Prosthetic vascular graft infection</td>
</tr>
<tr>
<td>Sternotomy wound infection</td>
</tr>
<tr>
<td>Mediastinitis</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
</tr>
<tr>
<td>Disseminated infection including embolic and immunologic manifestations (e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, cerebral vasculitis, pneumonia, myocarditis, hepatitis, nephritis)</td>
</tr>
</tbody>
</table>

---

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Culture negative PVE/ aortic graft infections
High index of suspicion for *M. chimaera* infections needed

How to diagnose it:

<table>
<thead>
<tr>
<th>Microbiology</th>
<th>New differential for “culture-negative”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive hirudin blood cultures for <em>M. chimaera</em></td>
<td>Brucella spp</td>
</tr>
<tr>
<td>Detection of <em>M. chimaera</em> by culture or PCR in cardiac tissue in the proximity of the prosthesis material</td>
<td>Coxiella burnetii</td>
</tr>
<tr>
<td></td>
<td>Bartonella spp</td>
</tr>
<tr>
<td></td>
<td>Tropheryma whippeli</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma spp</td>
</tr>
<tr>
<td></td>
<td>Legionella spp</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium chimaera</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of non-casating granulomas and foamy/pleomorphic macrophages within and outside the tissue in the proximity of the prosthesis material</td>
</tr>
</tbody>
</table>

Additional criteria:
Negative conventional blood cultures
SeroLOGY, exclusion of Coxiella, Bartonella, Brucella, Tropheryma whippeli, Legionella, Mycoplasma, Chlamydia

Presentation often atypical and delayed
Extracardiac manifestations of preceed cardiac manifestations

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Clinical presentation

- Cerebral vasculitis
- Pneumonitis
- Splenic emboli
- Bone marrow infection
- Chorioretinitis
- Blood
- Hepatitis
- Nephritis
- Osteomyelitis

Anterior and posterior uveitis/ chorioretinitis

51 year old male
Multifocal choroidal lesions

Multiple flat, cream colored lesions with indistinct border

Depending on the activity status of the lesion they appeared hyper- or hypoautofluorescent

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### Treatment

**Multidisciplinary approach**

- Infectious disease specialist
- Microbiologist
- Cardiovascular surgeon
- Cardiologist
- Cardiac anesthesia
- Nucelar imaging specialists
- Ophthalmologist

---

Ocular manifestations are good indicators of the systemic control of the disease process

Zweifel S et al. Di of Ophthalmology USZ

---

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lead-in phase:</th>
<th>Redo-Operation:</th>
<th>Chronic phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>Clarithromycin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Rifabutin</td>
<td>Rifabutin</td>
<td>Rifabutin</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>Ethambutol</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>+/- Amikacin</td>
<td>+/- Amikacin</td>
<td>+/- Amikacin</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>Moxifloxacin</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Goal:</td>
<td>Reduction of bacterial load</td>
<td>Removal of biofilm-forming</td>
<td>Treatment, hindrance of new</td>
</tr>
<tr>
<td></td>
<td></td>
<td>strains</td>
<td>dissemination</td>
</tr>
</tbody>
</table>

- **Break-through infections occur without removal of cardiac devices**
  - Embolic events
  - Epicardial left wire infection
  - Endocarditis

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---

**Table 3** Phenotypic drug susceptibility testing of 13 *M. chimaera* isolates of the 10 study patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample date</td>
<td>18.05.14</td>
<td>11.08.14</td>
<td>27.08.14</td>
<td>07.08.14</td>
<td>05.07.14</td>
<td>07.07.14</td>
<td>18.08.14</td>
<td>22.08.14</td>
<td>23.08.14</td>
<td>29.08.14</td>
</tr>
<tr>
<td>Material</td>
<td>Bone marrow</td>
<td>Bone</td>
<td>Blood</td>
<td>Cardiac tissue</td>
<td>Pocket swab</td>
<td>Ventricular blood</td>
<td>Cardiac tissue</td>
<td>Blood cultures</td>
<td>Blood cultures</td>
<td>Blood cultures</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
<td>≤5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
<td>&gt;1 – 10</td>
</tr>
<tr>
<td>Linezolid</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Data are minimum inhibitory concentrations, in mg/L.
ND: not done, due to low yield. Sputum samples, MNG.
RIF method applied in Patients 1–5; the broth dilution method was applied in Patients 7–10.

---

**Situation in vivo/ on prosthesis?**

---

**Prevention**

---

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Separating heater-cooler unit from operating room air


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Video of smoke experiments showing contamination of ultra-clean ventilation in OR

https://youtu.be/YZ41aLoHrhQ

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<table>
<thead>
<tr>
<th>Early diagnosis</th>
<th>Screening</th>
</tr>
</thead>
</table>

Screening tools

- Look for it!
- Physical examination
- Medical history
- Heparin blood cultures, Perform mycobacterial cultures or
- Mycobacterial specific PCR in case of biopsy
- Histopathological work up (presence of granulomas)
- Scrutinze Sarcodosis, vasculitis or unknown systemic diseases

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Look carefully at fever of unknown origin or vasculitis with former cardiopulmonary bypass surgery

**63 year-old lady**

2008 History of aortic valve replacement

Fatigue, fevers, and weight loss.

2011 Unknown vasculitis with 4/10 blood cultures positive for MAC

Retrospective review of echocardiography:

Endocarditis with strains

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Screening approach among patients with former cardiopulmonary bypass surgery

<table>
<thead>
<tr>
<th>Screening</th>
<th>Prosthetic valve endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended</td>
<td>Aortic graft infection</td>
</tr>
<tr>
<td>Recommended</td>
<td>Fever of unknown origin</td>
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<tr>
<td></td>
<td>Sarcoidosis,</td>
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<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Systemic disease of unknown cause</td>
</tr>
<tr>
<td>Recommended</td>
<td>Former heart transplantation</td>
</tr>
<tr>
<td>Not recommended</td>
<td>Former assist device in place</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

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A Webber Training Teleclass

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Global *Mycobacterium chimaera* Outbreak in Cardiac Surgery
Hugo Sax and Barbara Hasse, University of Zurich Hospital
Sponsored by the World Health Organization

Missed diagnosis….

Look back for MAC/ *M. avium* cases
Look back for culture-negative PVE, aortic graft infection

Look back yielded around 20 cases of presumptive cardiac infections with MAC with fatal outcome

Look back at University Hospital Zurich yielded no cases
Look back Switzerland: ongoing
Global *Mycobacterium chimaera* Outbreak in Cardiac Surgery

Hugo Sax and Barbara Hasse, University of Zurich Hospital

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The story is still ongoing…

Conclusions

When a system can fail, it will fail (Murphy)

A note on common sense

Medical devices are not grounded such as airplanes

Outbreak investigation on an international level is slow

We don’t know yet how big this is
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Take-home message:

Look for it!

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The next WHO teleclass ....
April 20, 2016

THE CORE COMPONENTS FOR INFECTION PREVENTION
AND CONTROL PROGRAMS AND ACTION PLAN

Jules Storr
Objectives:
- Outline the background and rationale
- Summarise the two-pronged approach
- Explore how the core components will contribute to the
global knowledge
- Describe next steps and highlight how this work will
  strengthen approaches to IPC improvement and
  implementation across all countries

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