M. chimaera outbreak in cardiac surgery
Zurich, Switzerland, where it all begun

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Specific questions by FDA

When did it become obvious that this is a hospital outbreak?
What were the control efforts?
What is the necessary lab capacity to detect *M. chimaera*?
Information strategy for potentially infected cardiac surgery patients?
Consent form modifications for cardiac surgery patients?
Virulence of *M. chimaera* versus MAC or other NTM?
Prosthetic Valve Endocarditis and Bloodstream Infection Due to *Mycobacterium chimaera*

Yvonne Achermann, a Matthias Rössle, b Matthias Hoffmann, c Vanessa Deggim, d Stefan Kuster, a Dieter R. Zimmermann, b Guido Bloemberg, d Michael Hombach, d Barbara Hasse a

Division of Infectious Diseases and Hospital Epidemiology, University and University Hospital Zurich, Zurich, Switzerland; Institute of Clinical Pathology, University and University Hospital Zurich, Zurich, Switzerland; Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland

Prosthetic valve endocarditis (PVE) due to fast-growing nontuberculous mycobacteria (NTM) has been reported anecdotally. Reports of PVE with slowly growing NTM, however, are lacking. We present here one case of PVE and one case of bloodstream infection caused by *Mycobacterium chimaera*. Randomly amplified polymorphic DNA (RAPD)-PCR indicated a relatedness of the two *M. chimaera* strains. Both patients had heart surgery 2 years apart from each other. A nosocomial link was not detected.
Case #1 | 58-year-old male

2008 Mitral annuloplasty ring

2010 Dx of systemic sarcoidosis with unspecific multi-organ granulomatous inflammation > Prednision 20mg > 50mg, but deteriorated

2011 Respiratory distress, severe mitral and aortic valve insufficiency, at surgery fraying of ring and valve destruction…
FIG 1. Histopathological analysis of valve tissue from patient 1. (a) Overview of the necrotic valve tissue (×) with granulocytic demarcation (arrows) and foamy macrophages (arrowheads) (hematoxylin and eosin [H&E] stain); (b) swollen foamy macrophages (H&E stain); (c) presence of numerous acid-fast bacilli (Ziehl-Neelsen stain).

- granulocytic demarcation
- necrotic value tissue
- foamy macrophages
- acid-fast bacilli
Case #2 | 51-year-old man

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

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

Rx: clarithromycin, rifabutin, and ethambutol

2012 Exodus due to splenic rupture
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-FP (A) and OPA18 (B). MW, molecular weight marker.
Surgical site infection with non-tuberculous mycobacteria
Outbreak investigation from 2013

Observations
Video analysis
Interviews
Workflow analysis
Mycobacteria cultures

Patient heating blanket water circuit
Heater-cooler unit water tanks/circuits
Showers
Drinking water fountains
Observations
Video analysis
Interviews
Workflow analysis
Mycobacteria cultures

Patient heating blanket water circuit
Heater-cooler unit water tanks/circuits
Showers
Drinking water fountains
Cardioplegia circuit

Patient blood circuit

Heart-lung-machine

Heater-cooler-unit

Airflow

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Heat-exchangers

Cardioplegia solution

Patient blood circuit

HumanLabZ.org

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Sorin Stockert T3
Air cultures with heater-cooler unit turned ON
Air cultures with heater-cooler unit turned OFF
Air cultures with heater-cooler unit turned ON

Air cultures with heater-cooler unit turned OFF
In the operating theatre

- contaminated, ON
- not contaminated, ON
- contaminated, OFF

Air cultures $\rightarrow$ positive
Air cultures $\rightarrow$ negative
Air cultures $\rightarrow$ negative
Randomly amplified polymorphic DNA PCR (RAPD-PCR)

Diagnostic challenges

**Water:** 50ml, centrifuge, decontamination with NALC-OH, BD MGIT Liquid Culture System + Solid Agar (Middlebrook 7H11), 25/90$

**Air:** demanding: each germ inspected, then 16S-rDNS-sequencing CLSI or MALDI-TOF-MS and Bruker Biotyper Search

Reference centres for Mycobacteria in Europe can do this.
Case definition

A case was defined as a patient with proven invasive *M. chimaera* infection following open-chest heart surgery performed at the hospital since August 2006.
Patients with *M. chimaera* infection in Zurich, Switzerland

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Year of index surgery</th>
<th>Latency surgery-Dx (years)</th>
<th>Type of cardiac surgery</th>
<th>Implant</th>
<th>Material</th>
<th>Manifestations</th>
<th>Positive cultures for M. chimaera</th>
<th>Histopathology</th>
</tr>
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<tbody>
<tr>
<td>Patient 1 †</td>
<td>58</td>
<td>2008</td>
<td>2.9</td>
<td>Mitral valve reconstruction</td>
<td>28 mm C-E physio mitral annuloplasty ring</td>
<td>Layers of Elgiloy Sewing ring with layers of silicone covered by polyester knit fabric</td>
<td>Endocarditis, pancytopenia, hepatitis, renal involvement</td>
<td>Blood, cardiac tissue prosthesis, sputum</td>
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<td>Patient 2 †</td>
<td>51</td>
<td>2010</td>
<td>1.5</td>
<td>Composite graft for aortic dissection</td>
<td>25 mm ATS composite graft 8 mm GAHE Gelweave x prosthesis</td>
<td>Heart valve: pyrolytic carbon; Graft: double woven velour; Hemashield woven polyester</td>
<td>bloodstream infection, splenomegaly, pancytopenia, hepatitis, pulmonary, ocular emboli</td>
<td>Blood, sputum, bone marrow, urine</td>
<td>Granulomatous myocarditis, pneumonitis, nephritis involvement of spleen</td>
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<td>Patient 3</td>
<td>64</td>
<td>2009</td>
<td>3.6</td>
<td>Mitral valve reconstruction</td>
<td>32 mm x 2 mm Carpentier ring</td>
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<td>Endocarditis, wrist arthritis, pancytopenia, splenomegaly, hepatitis, renal Impairment, ocular emboli</td>
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<td>Patient 4</td>
<td>49</td>
<td>2009</td>
<td>3.4</td>
<td>Aortic valve replacement</td>
<td>24 mm ATS Open Pivot AP Series Heart Valve</td>
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<td>ATS AVG 26 mm graft as elephant trunk</td>
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<td>Vascular graft infection, splenomegaly, hepatitis, renal failure, multifocal choroiditis</td>
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2008 - 2014

6 infected patients

3000 open-chest heart surgery interventions
Switzerland investigation in 2014

16 cardiac surgery centres

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

No additional patient at that time
Tödliche Infektionen: Zürcher Unispital entdeckt Bakterium


Tödliches Bakterium im Zürcher Unispital

Dienstag, 15. Juli 2014, 18:54 Uhr, aktualisiert um 19:58 Uhr

Das Zürcher Universitätsspital hat ein Bakterium entdeckt, welches bei Herzoperationen zu Komplikationen oder im schlimmsten Fall sogar zum Tod führen kann. Es befindet sich im Leitungswasser und ist im Normalfall ungefährlich.

Tödliche Infektionen nach Herzoperationen

Zwei Patienten starben an den Folgen der Infektion. (Bild: Keystone/Symbol)

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

Philipp Kohler¹, Stefan P. Kuster¹, Guido Bloemberg², Bettina Schulthess²,³, Michelle Frank⁴, Felix C. Tanner⁴, Matthias Rösle⁵, Christian Böni⁶, Volkmar Falk⁷,⁸, Markus J. Wilhelm⁷, Rami Sommerstein¹, Yvonne Achermann¹, Jaap ten Oever⁹, Sylvia B. Debast¹⁰, Maurice J.H.M. Wolfhagen¹⁰, George. J. Brandon Bravo Bruinsma¹¹, Margreet C. Vos¹², Ad Bogers¹³, Annerose Serr¹⁴, Friedhelm Beyersdorf¹⁵, Hugo Sax¹, Erik C. Böttger²,³, Rainer Weber¹, Jakko van Ingen¹⁶, Dirk Wagner¹⁷, and Barbara Hasse¹⁸*
10 patients (Switzerland, Germany, Netherlands)
1-4 years latency since cardiac implant surgery
Peripheral or systemic manifestations
8 of 10 surgical re-intervention despite Rx
6 of 10 break-through infections, 4 fatal
3 patients are being monitored post-Rx
European Centre for Disease Prevention and Control. EU protocol for case detection, laboratory diagnosis and environmental testing of *Mycobacterium chimaera* infections potentially associated with heater-cooler units: case definition and environmental testing methodology. Stockholm: ECDC; 2015
Experience with cases
Biopsy cultures test negative after 9 months under AB Rx and multiple debridements
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Dienstag, 15. Juli 2014, 19:04 Uhr, aktualisiert um 19:08 Uhr

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Tödliches Bakterium im Zürcher Unispital

3:05 min, aus Schweiz aktuell vom 15.7.2014

Tagblatt Online, 14. Juli 2014, 17:36 Uhr

Tödliche Infektionen nach Herzoperationen

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HumanLabZ.org

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Experience with cases
Biopsy cultures test negative after 9 months under AB Rx and multiple debridements
M. chimaera still grows after 1 year of AB Rx
Intensified (Zurich) protocol

Daily water changes from 2014
Separating heater-cooler unit from operating room air
Conclusions

When a system can fail, it will fail (Murphy)
A note on common sense (water, airflow)
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
When did it become obvious that this is a hospital outbreak?

A: 2013/14

What were the control efforts?

A: Daily water changes, air separation (housing)

What is the necessary lab capacity to detect *M. chimaera*?

A: Mycobacteria reference centres

Information strategy for potentially infected cardiac surgery patients?

A: Media, treating physicians

Consent form modifications for cardiac surgery patients?

A: No, no risk anymore

Virulence of *M. chimaera* versus MAC or other NTM?

A: Yet unknown
Take-home message:

Look for it!