



# Epidemiología, diagnóstico y tratamiento de las infecciones por *Mycobacterium chimaera*

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# Outline



**Scope of the problem**  
Diagnosing a clinical case  
Clinical management



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

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Six heart surgery patients with *M. chimaera* endocarditis, aortic graft infection, bacteremia

Water sources (HCU) and drinking fountains contaminated with *M. chimaera*

Air samples detected *M. chimaera*



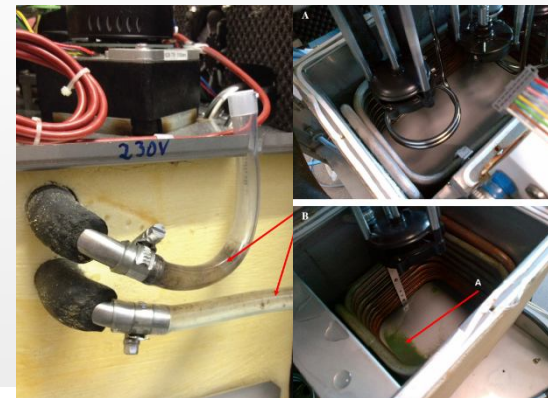
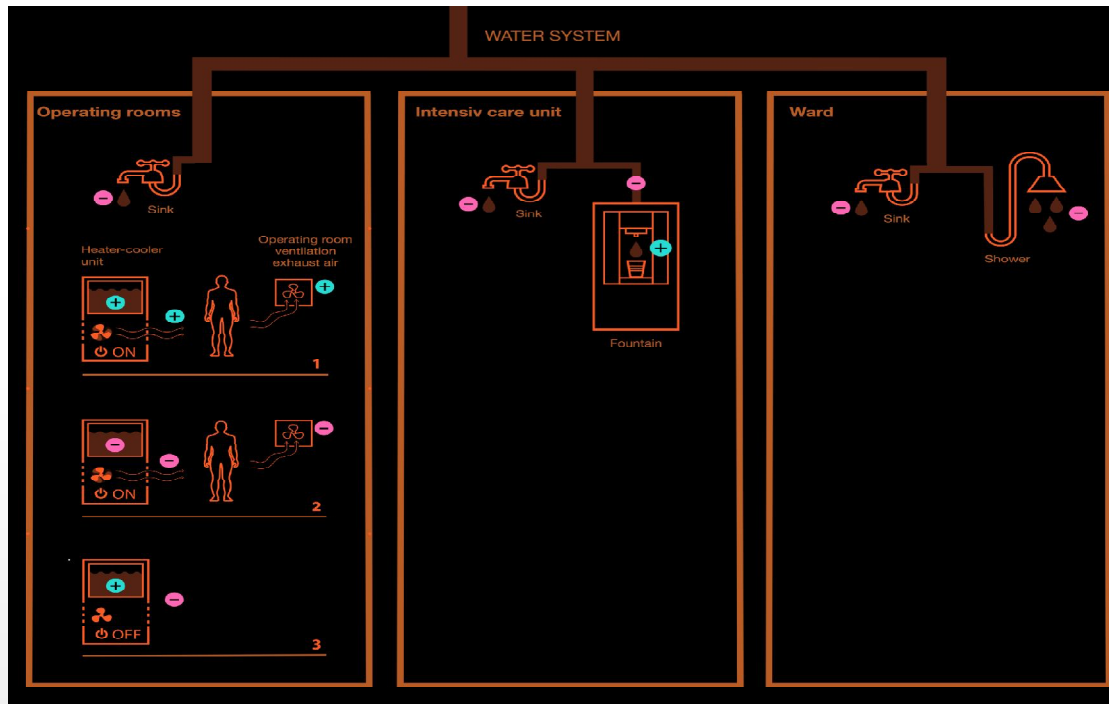
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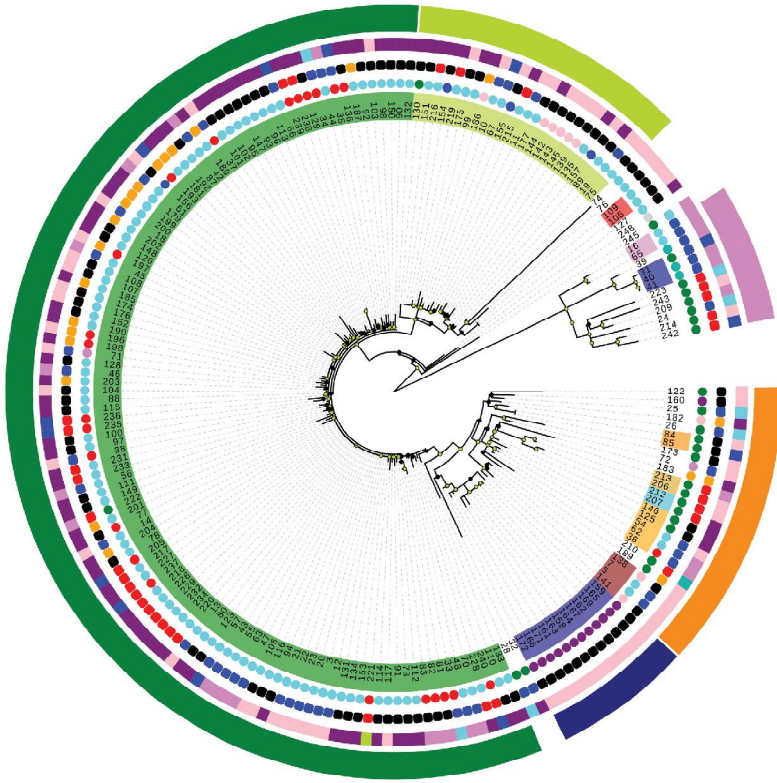
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Sax H, Bloemberg G, Hasse B et al.  
Clin Infect Dis 2015; 61(1):67-75

# The role of Heater cooler units (HCU)



# Association of human cases with Stockert 3T HCU



**FDA U.S. Food and Drug Administration**  
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Department of Health and Human Services

Public Health Service  
Food and Drug Administration  
10903 New Hampshire Avenue  
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Silver Spring, MD 20993

DEC 29, 2015

WARNING LETTER

<http://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm479684.htm>



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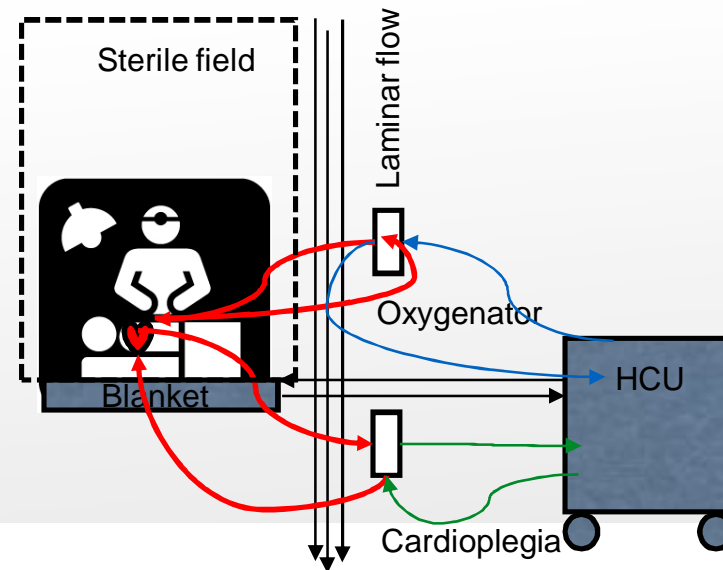
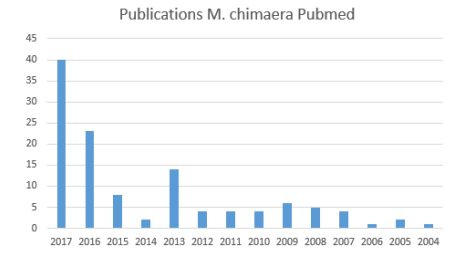


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Haller et al Eurosurveillance, 2016; Perkins KM et al. MMWR Morb Mortal Wkly Rep. 2016 Oct 14;65(40):1117-1118  
Chand et al. Clin Infect Dis. 2017 Feb 1;64(3):335-342; Williamson D et al N Engl J Med 2017 Feb 9;376(6):600-602  
Van Ingen et al. Lancet Infect Dis. 2017 Jul 12. pii: S1473-3099(17)30324-9

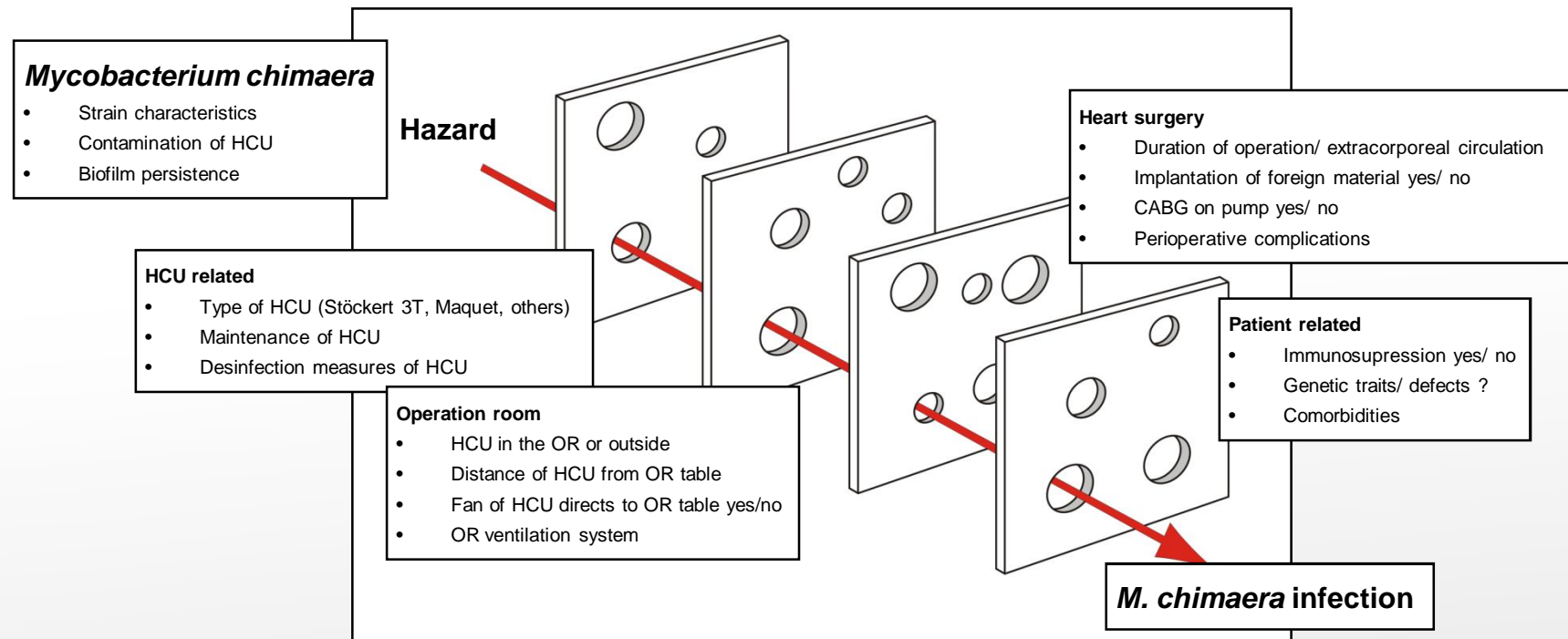
# Heater Cooler Units: Scope of the problem

- Are a key component of open cardiac procedures
- If withdrawn capacity of life-saving cardiac surgery affected
- Contamination at factory/ locally/ cross contamination
- Biofilm persistence of mycobacteria
- Implicated devices are widely distributed
- Global outbreak problem
- Air management problem in OR





# The stochastic phenomenon of getting the infection

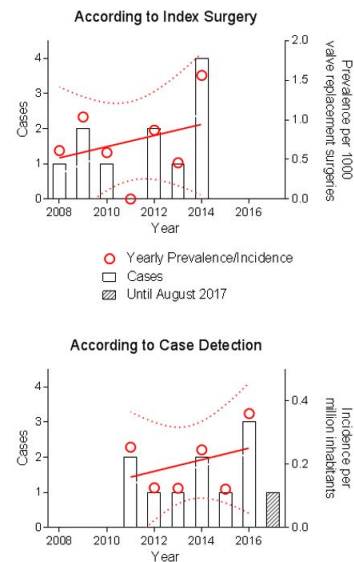


# The risk of getting the infection is low

## Switzerland

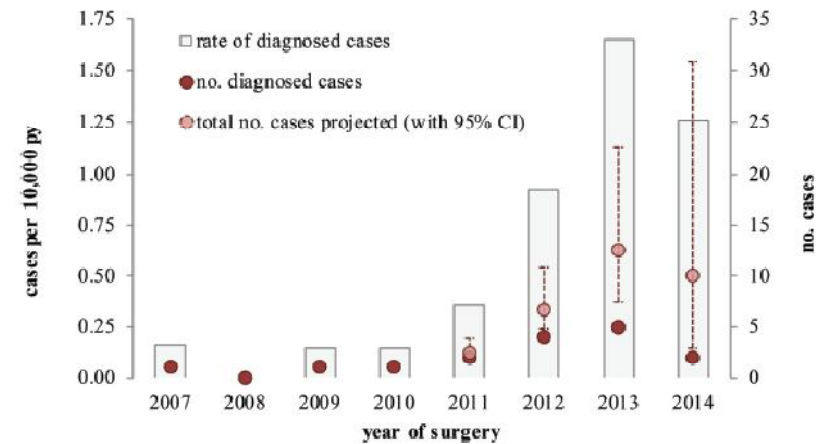
Yearly incidence: 0.16-0.25 cases per 1 million Swiss inhabitants

Prevalence: 0.52-0.94 cases per 1000 valve replacement surgeries



## UK

0.39 cases per 10,000 PY



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Sommerstein R et al. unpublished  
Chand et al. Clin Inf Dis 2017



# Current global situation



## Clinical cases

|              |            |
|--------------|------------|
| Australia    | 6          |
| Belgium      | 0          |
| Canada       | 4          |
| China        | 2          |
| CH           | 11         |
| D            | 6          |
| DK           | 0          |
| NL           | 4          |
| France       | 2          |
| Ireland      | 4          |
| Spain        | 3          |
| USA          | 70         |
| UK           | 25         |
| <b>Total</b> | <b>137</b> |

Medical Device Reporting: 86 patients

339 MDR reports (99 facilities, 5 HCU manufacturers)

September 29th, 2017.

(To the best of my knowledge)



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## 66-year old man

Implantation of hip prosthesis 2000

Aortic valve and arch replacement 2013

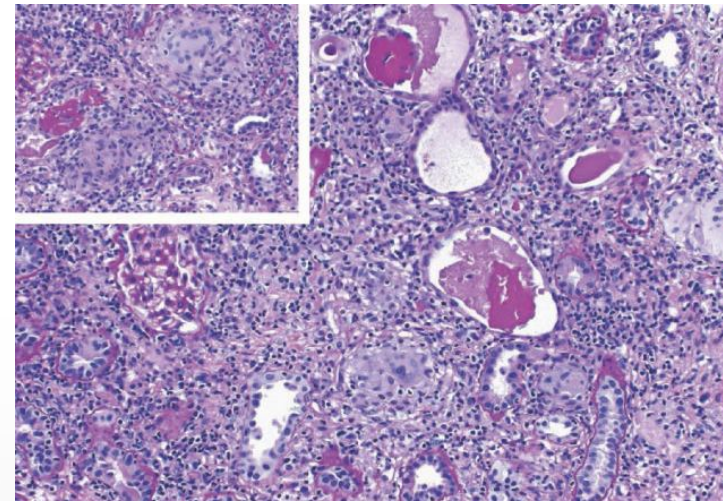
Presentation in 2016:

Asthenia, night sweats, weight loss (-12kg)

Laboratory: CRP 33 mg/l, Creatinine 530  $\mu\text{mol/l}$

Pancytopenia

→ Diagnosis of Sarcoidosis



Kidney biopsy: Tubulointerstitial nephritis with several non caseating granulomas

Bone marrow biopsy: normal erythro- and myelopoiesis, no malignant process



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# Possibility of a disseminated *M. chimaera* infection?

**Table 3** Recommendations for future case detection

Exposure criteria

A patient having undergone surgery requiring cardiopulmonary bypass prior to symptoms of infection

Clinical criteria

Prosthetic valve endocarditis

Prosthetic vascular graft infection

Sternotomy wound infection

Mediastinitis

Fever of unknown origin + **Sarcoidosis, Vasculitis**

Disseminated infection including embolic and immunologic manifestations (e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, cerebral vasculitis, pneumonitis, myocarditis, hepatitis, nephritis)

## Caveat:

*“When you hear hoofbeats, think horses not zebras.”*



# Diagnostics

## Microbiology

Positive heparin blood cultures for *M. chimaera*

Detection of *M. chimaera* by culture or PCR in cardiac tissue in the proximity of the prosthetic material

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## Histopathology

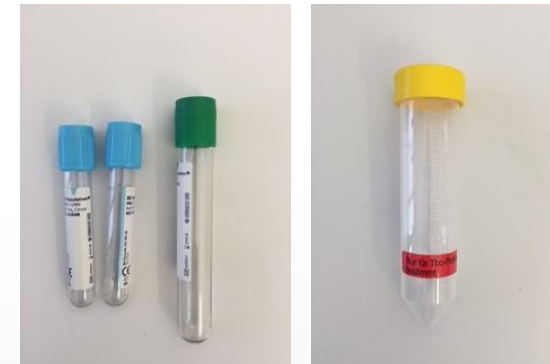
Detection of non-caseating granuloma and foamy/swollen macrophages with/without acid fast bacilli in cardiac tissue in the proximity of the prosthetic material

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## Additional criteria

Negative conventional blood cultures

Serologic exclusion of *Coxiella*, *Bartonella*, *Brucella*, *Tropheryma whippeli*, *Legionella*, *Mycoplasma*, *Chlamydia*



2 x citrate tubes

Native tube

**or**

1 x heparin tube

BD BACTEC™ Myco/F Lytic flasks

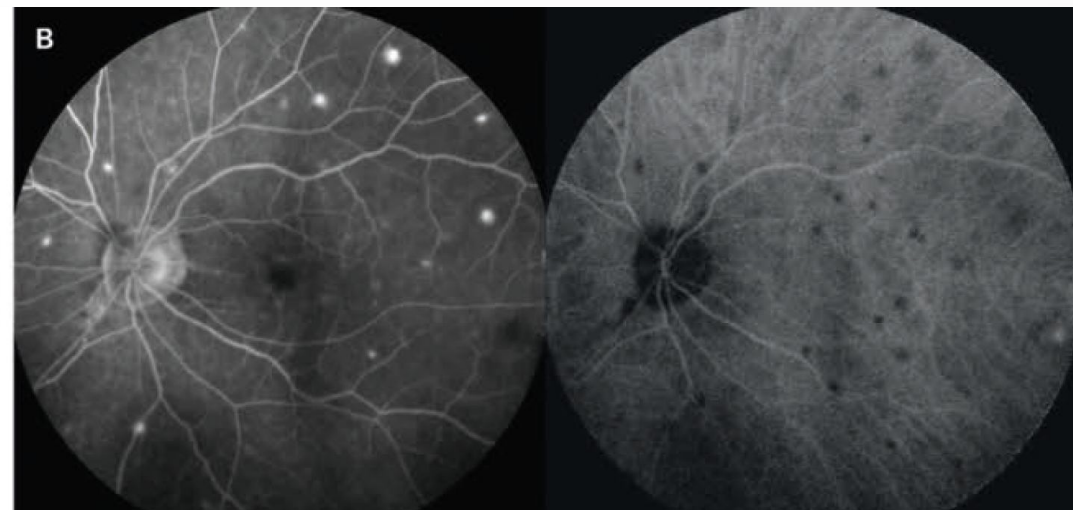


## Diagnosis: disseminated *M. chimaera* infection associated with cardiac surgery (proof by WGS – ‘related’ patient)

Heparin blood cultures positive after 4 weeks for *M. chimaera*

Mycobacterial PCR from kidney and bone marrow biopsy negative.

Eye examination: multifocal chorioretinitis



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## Challenges in diagnosis: highlighted in this case



Know the disease!

- Latency between index surgery and symptoms
- Non specific nature of presentation
- Standard bacterial cultures poorly sensitive  
    → Heparin cultures
- Often misdiagnosed in the beginning
- (Need of directed mycobact. testing)



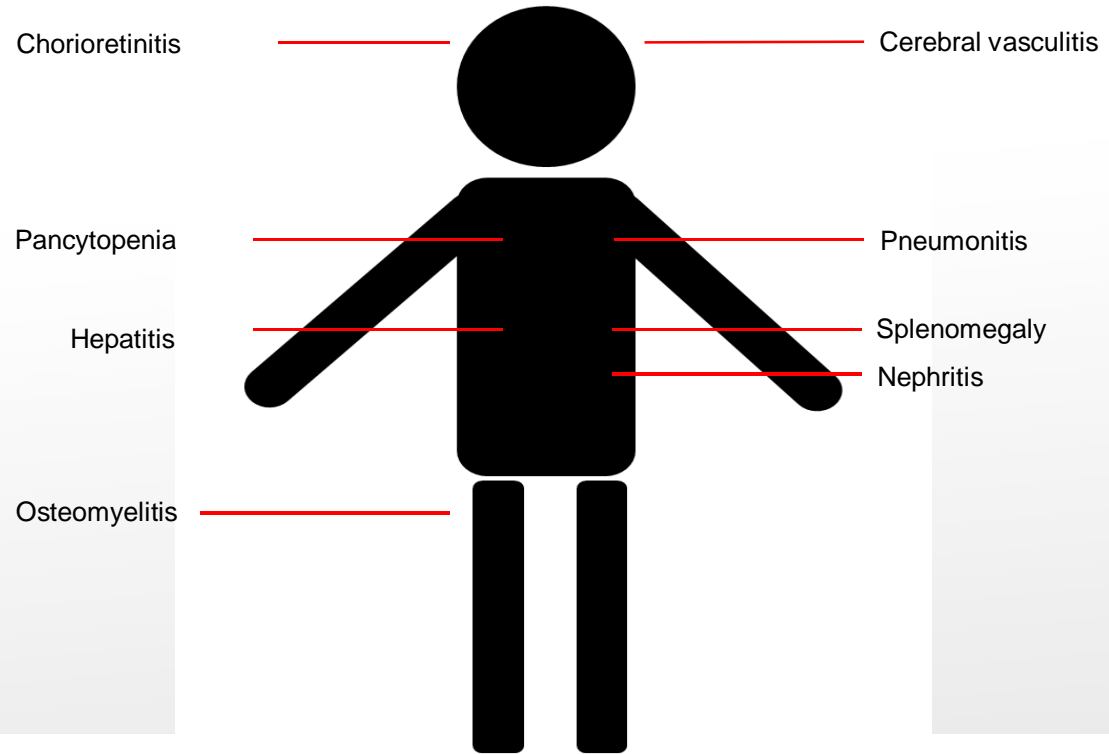
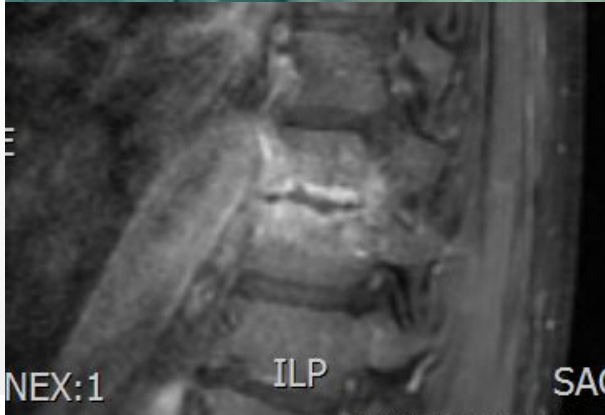
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# Extracardiac manifestations may precede cardiac manifestations



# Dangers for misdiagnosis

## New differential for „culture negative“

|                        |
|------------------------|
| Brucella spp           |
| Coxiella burnetii      |
| Bartonella spp         |
| Tropheryma whipplei    |
| Mycoplasma spp         |
| Legionella spp         |
| Mycobacterium chimaera |

- Sarcoidosis
- FUO
- Vasculitis
- Culture negative PVE and PVGI
- False detection as MAC/ *M. intracellulare*



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# Treatment for „clonal disease“: Macrolide + companion drugs

**Table 1** Phenotypic drug susceptibility testing of 15 *M. chimerae* isolates of the 10 study patients

| Patient        | 1           | 2           | 3         | 4        | 5           | 6              | 7             | 8              | 9        | 10             | 11            | 12           | 13           | 14       | 15             |
|----------------|-------------|-------------|-----------|----------|-------------|----------------|---------------|----------------|----------|----------------|---------------|--------------|--------------|----------|----------------|
| Sample site    | 10.06.11    | 27.07.11    | 10.09.11  | 20.09.11 | 07.07.14    | 06.09.11       | 11.06.11      | 06.01.14       | 00.09.14 | 14.01.14       | 26.10.14      | 17.06.11     | 27.04.11     | 16.01.11 | 00.01.11       |
| Material       | Mitral ring | Bone marrow | Urine     | Bone     | Mitral ring | Cardiac shower | Pocket shower | Vertebral bone | Urine    | Cardiac shower | Blood culture | Aortic valve | Mitral valve | Bone     | Cardiac shower |
|                | MIC (mg/L)  |             |           |          |             |                |               |                |          |                |               |              |              |          |                |
| Clarithromycin | ≤0.4        | ≤0.4        | ≤0.4      | ≤0.4     | ≤0.4        | ≤0.4           | ≤0.4          | ≤0.4           | ≤0.4     | ≤0.4           | ≤0.4          | 2            | 1            | 2        | 0.5            |
| Moxifloxacin   | 2.5         | 2.5         | 2.5       | 2.5      | 2.5         | 0.5            | 0.5           | 2.5            | 2.5      | 2.5            | 2.5           | 1            | 1            | 1        | 2              |
| Linezolid      | ND          | ND          | ND        | 4        | 16          | ND             | 16            | 4              | 4        | 16             | 16            | 16           | 8            | 16       | 16             |
| Amikacin       | 20          | 20          | 20        | 4        | 4           | 4              | 4             | 4              | 4        | 4              | 20            | 8            | 8            | 8        | 8              |
| Mikampicin     | ≤0.1-0.2    | ≤0.1-0.2    | ≤0.1-0.2  | 4        | 4           | ND             | 4             | 4              | 4        | 4              | 4             | 2            | 2            | 2        | 1              |
| Rifabutin      | ≤0.01-0.2   | ≤0.01-0.2   | ≤0.01-0.2 | 0.4      | 0.4         | 2              | 0.4           | 0.4            | 0.4      | 2              | 2             | 0.5          | 0.5          | ≤0.05    | 0.5            |
| Ethambutol     | ≤5          | ≤5          | ≤5        | ≤5       | ≤5          | ND             | 12.5          | ≤5             | ≤5       | 12.5           | 12.5          | 8            | 8            | 4        | 8              |

Data are minimum inhibitory concentrations, in mg/L.  
 ND, not done; minimum inhibitory concentrations, MICs.  
 MIC75 method applied in Patients 1-3, the break dilution method has been applied in Patients 7-10.

Companion drugs: ethambutol, rifabutin/rifampicin, amikacin, moxifloxacin  
*in vitro* testing

- Recommended for clarithromycin
- Role for routine testing for rifampicin, rifabutin, amikacin, ethambutol, moxifloxacin?

## Potential role of other antimicrobials not yet established

| Medication                      | MIC INH Mikrodil. day 7 [mg/L] | MIC INH Mikrodil. day 14 [mg/L] | MIC INH Mikrodil. day 21 [mg/L] |
|---------------------------------|--------------------------------|---------------------------------|---------------------------------|
| Rifampicin                      | 0.0625-0.25                    | 0.5-1                           | 2                               |
| Rifabutin                       | 0.015                          | 0.061-0.125                     | 0.125                           |
| Moxifloxacin                    | 0.5                            | 0.5-1                           | 1                               |
| Amikacin                        | 2-4                            | 2-4                             | 4                               |
| Kanamycin                       | 2                              | 4                               | 4                               |
| Clofazimin                      | 0.25-1                         | 0.5-1                           | 0.5-1                           |
| Dalamanid                       | 1                              | 2-4                             | 4-8                             |
| Bedaquilin                      | <0.015                         | 0.03                            | 0.03-0.06                       |
| Clarithromycin                  | 0.5                            | <0.5                            | 0.5                             |
| Imipenem                        | 8                              | 32                              | 128                             |
| Meropenem                       | 4-8                            | 8-16                            | 32                              |
| Meropenem and Clavulanic acid   | <0.5                           | 4                               | 16                              |
| Amoxicillin and Clavulanic acid | 0.5-2                          | 4-8                             | 16-32                           |
| Sutezolid                       | 0.5-1                          | 0.5-1                           | 1                               |

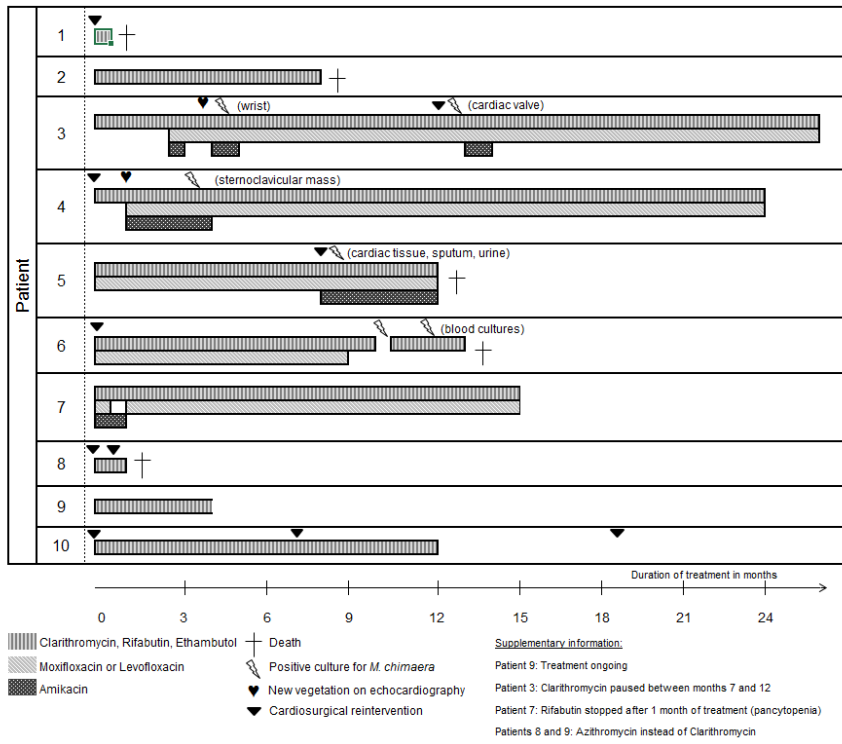
MIC of Zurich-1 strain

Promising results

- Bedaquilin
- Beta Lactam/ Clavulanic acid



# Frequent treatment failures in early patients



No response after 6 months of approp. therapy  
Break through infections

Exclusion of:

- Medication nonadherence
- Emergence of a macrolide-resistant isolate



## A three step treatment approach for disseminated infection

### Lead-in phase:

Tuberculostatic  
treatment

Goal:  
Reduction of  
bacterial load

### Redo-Operation:



Goal:  
Removal of biofilm-  
forming strains

### Chronic phase:

Tuberculostatic  
treatment

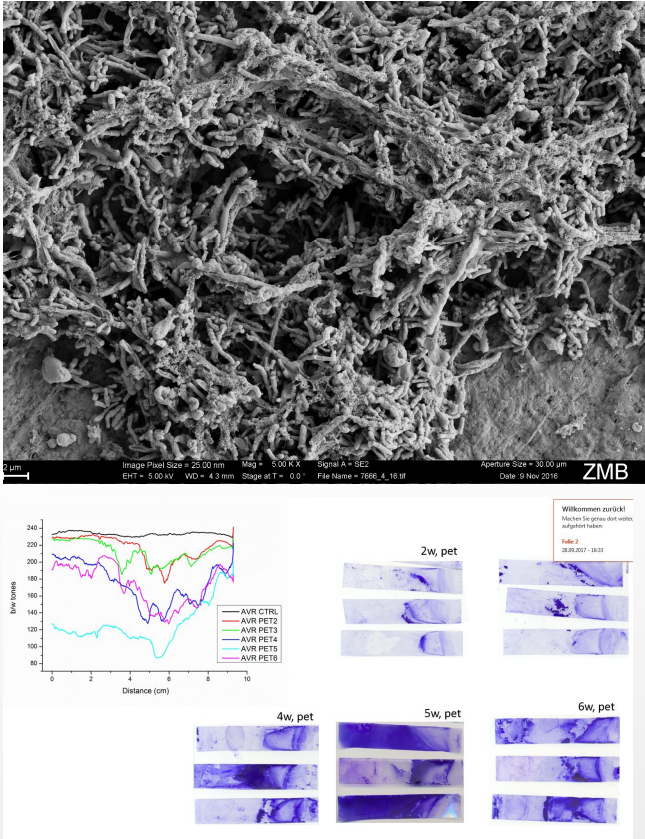
Goal:  
Treatment, hindrance of  
new dissemination





# Outcome better with „redo“-surgery

|  | US experience |         | European experience |          |
|--|---------------|---------|---------------------|----------|
|  | Patients      | Deaths  | Patients            | Deaths   |
| Antibiotics and removal of prosthetic material | 6 (100%)      | 2 (33%) | 8 (100%)            | 4 (33%)  |
| Antibiotics only                               | 14 (100%)     | 6 (43%) | 2 (100%)            | 2 (66%)  |
| No antibiotics                                 | 4 (100%)      | 3 (75%) | 0 (100%)            | 0 (0.0%) |
| Overall  | 24 (100%)     | 11 (46) | 10 (100%)           | 6 (60%)  |



Courtesy to C. Fabbri, Institute of Plant Biology, UZH



## 66 year old men – Outcome

Tuberculostatic treatment.

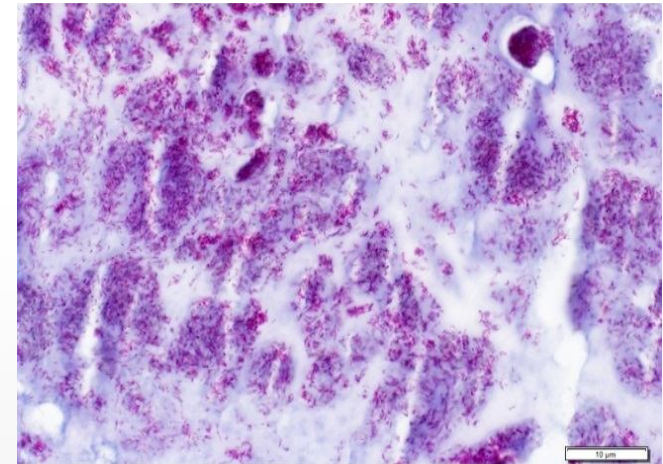
- Clarithromycin, rifabutin, ethambutol, moxifloxacin
- No amikacin.

Immunereconstitution inflammatory syndrome

- Worsening kidney function after start of treatment

Cardiac surgery

- Replacement of all foreign material
- Placement of a homograft.



Acid fast stain from resected composite aortic graft

Break through infection 06/2017

*M. chimaera* infection from Prosthetic joint infection



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Erb et al, Swiss Medical Forum 2017

## Outcome European patients revisited...

|  | Total patients | Death    | Break through infection | Stop of therapy | Relapse   |
|--|----------------|----------|-------------------------|-----------------|-----------|
| Antibiotics Removal of prosthetic material | 16 (100%)      | 5 (30%)  | 10 (63%)                | 4 (19%)         | 1/4 (25%) |
| Antibiotics only                           | 4 (100%)       | 4 (100%) | 4 (100%)                | na              | na        |
| Overall                                    | 21 (100%)      | 9 (45%)  | 14 (67%)                | 4 (20%)         | 1 (25%)   |
| Localized wound infection, No antibiotics  | 1 (100%)       | 0 (0%)   | 0 (0%)                  | 1 (100%)        | na        |

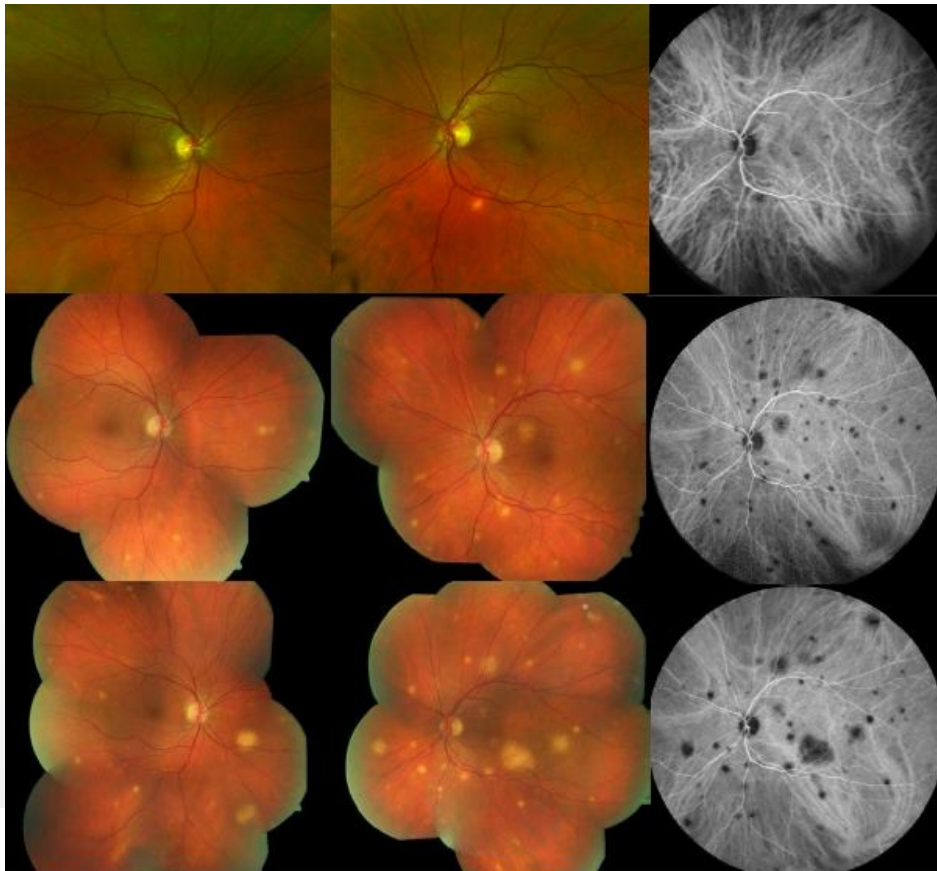


## Challenging treatment issues for the clinician

- Is stopping of antimicrobial therapy feasible?
- Optimal treatment regimen for disseminated disease?
- Correlation between treatment response and *in vitro* susceptibility of the patient's isolate to anti-TB drugs?
- Correlation with the number of drugs in the treatment regimen to which isolate showed *in vitro* susceptibility?
- Role of therapeutic drug monitoring?



# Ocular manifestations: good indicators of disease control



With courtesy to Christian Boeni, USZ

# Conclusions



## Global HCU related outbreak

- When a system can fail, it will fail (Murphy)
- Outbreak investigation ongoing
- We don't know yet how big this is

## Clinical cases

- Many uncertainties
- Need of a patient case registry





## CH Collaboration

Guido Bloemberg  
Erik C Böttger  
Leo Eberl  
Stefan Erb  
Friedrich Eckstein  
Carlotta Fabbri  
Peter Graber  
Michael Greiner  
Maximilian Halbe  
Matthias Hoffmann  
Peter Keller, Philipp Kohler  
Christian Rüegg  
Peter Sander  
Hugo Sax  
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Bettina Schulthess  
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Rami Sommerstein  
Andreas Widmer

## International Collaboration

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D: Thomas Kohl, Katharina Krantzer,  
Stefan Niemann, Dirk Wagner, Volkmar Falk  
NL: Jakko van Ingen  
Ir: Margaret Hannan  
Spain: J. Miro Moreno  
US: Dan Diekema, Cindy Whitener, Chuck Daily  
Australia: Kate Clezy, Andrew Stewardson  
CDC: Heather Moulton, Lyman Meghan  
ECDC: Diamantis Plachouras



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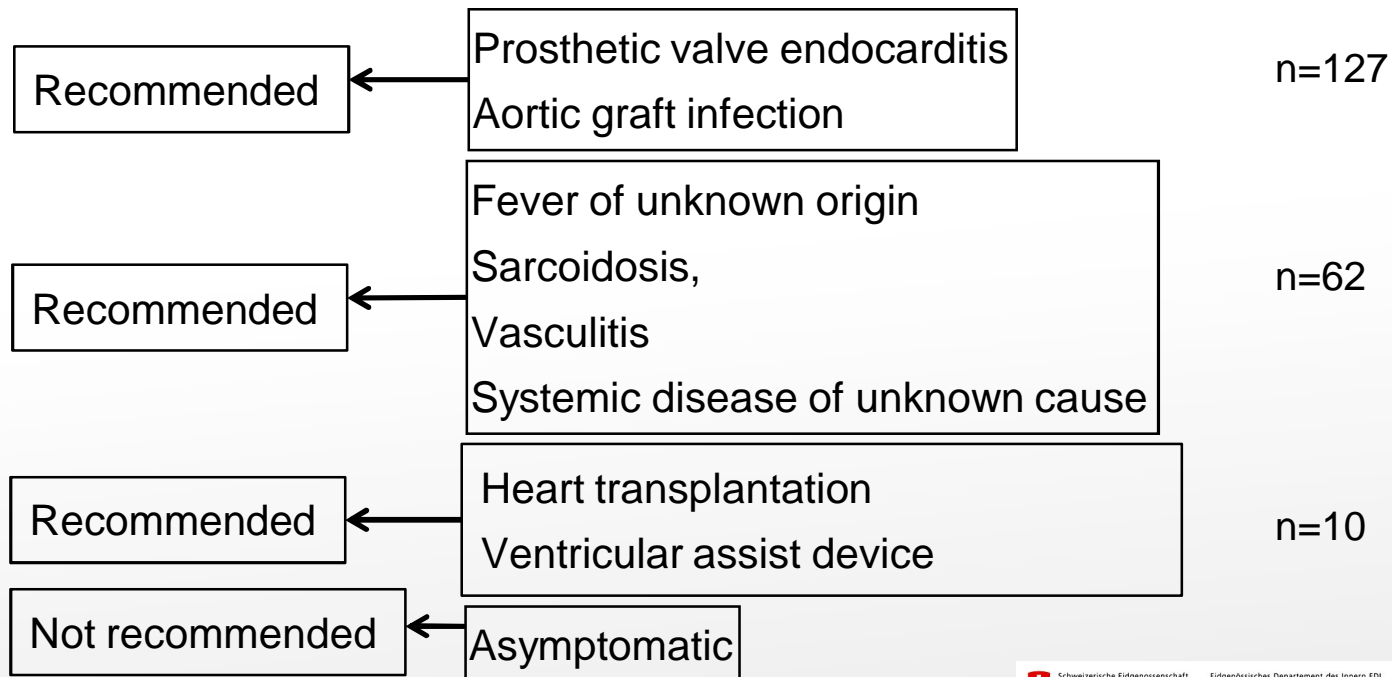


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Treating physicians/ patients/ relatives



# Which persons need to be screened for *M. chimaera*



 Schweizerische Eidgenossenschaft  
Confédération suisse  
Confederazione Svizzera  
Confederaziun svizra

 Eidgenössisches Departement des Innern EDI  
Bundesamt für Gesundheit BfG

Infektion mit *Mycobacterium chimaera* nach  
Chirurgie am offenen Herzen: Wann sollte man  
Patienten für Abklärungen überweisen?



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Swiss Chimaera Collaborative Jan 2017

# Challenges in diagnosis

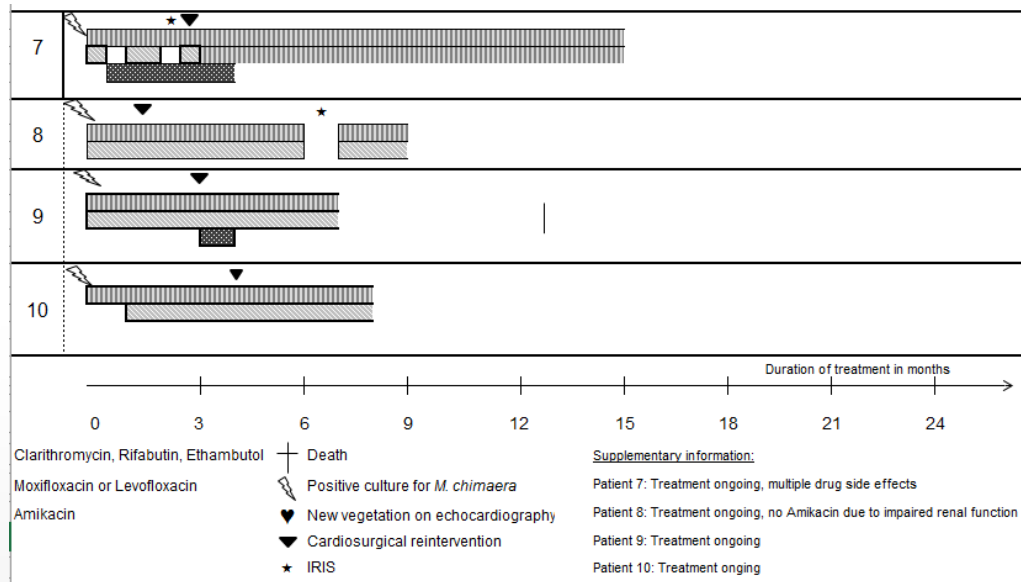


Pattern recognition

- Know the disease !
- Latency between index surgery and symptoms
- Non specific nature of presentation
- Standard bacterial cultures poorly sensitive  
    —→ Heparin cultures
- Need of directed mycobacteriological testing
- Often misdiagnosed in the beginning



## «New» Swiss cases



**No positive *M. chimaera* cultures after redo surgery**

- Latency: 28 month
- Follow up time: 10.5 months

Redo-Operation: 3 month after diagnosis



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Stefan Erb, Peter Graber, Andreas Widmer, personal communications