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


**Background / Introduction**

- A growing number of reports of cardiosurgical site infections due to non-tuberculous mycobacteria (NTM) have been reported, all isolates were fast-growing mycobacteria.
- In 2013 the authors published two cases (PVE and bloodstream infection) with *M. chimaera* (slowly growing, belongs to the *M. avium*-complex).
- During an outbreak at the Zurich Heart Center, *M. chimaera* was cultured from air sampling in the operating theatre and from water tanks of heater-cooler units serving the heart-lung machine. Similar fingerprints indicated that patients were infected during operation due to airborne transmission of microorganisms sprayed from the ventilation outlet of the heater-cooler unit (HCU) ([Sax H. et al.](https://cid.oxfordjournals.org/content/61/1/1.full))

**Prolonged outbreak of Mycobacterium chimaera infection after open-chest heart surgery, CID 2015:61 (1 July).**

- Six cases were identified in Zürich, and 4 cases in Freiburg (DE), Zwolle and Rotterdam. On 30 April 2015, an alert was published by the European Centre for Disease Prevention and Control (ECDC).
- The aim of the study is a comprehensive description of the clinical manifestations and outcome to these 10 cases. In addition exposure criteria and case definitions are presented for this novel disease entity.

**Methods**

**Exposure criteria:** Former open-heart surgery and implantation of cardioascular implant  
**Clinical criteria:** PVE, Prosthetic vascular graft infection, or disseminated infection

**Case definition**

1 Confirmed cases  
Cases including exposure and clinical criteria and *M. chimaera* proven by culture or PCR identification from invasive samples of the cardiac surgery site.

2 Probable cases  
Cases including exposure and clinical criteria. In addition detection of *M. chimaera* or *M. avium*-complex in blood and/or extracardiac tissue cultures.

**Case finding**

- Mycobacterial culture are not part of the routine workup in cardiovascascal infections.  
- 1 case: positive histopathology followed by genus-specific PCR  
- Remaining cases: Broad-range bacterial PCR (part of 16S rRNA gene) of cardiac tissue, bone or positive blood culture for mycobacteria
Detection of *M. chimaera*
- Mycobacterial culture using MGIT 960 and Middlebrook 7H11 agar plates
- Direct broad-range bacterial PCR and sequencing
- Antimicrobial susceptibility testing with MGIT 960 with TB Exist module (strains from Zürich)

Clinical investigations
- Comorbidities quantified with Charlson index
- ASA score, type of operation, extracorporeal circulation time, modified Duke criteria were assessed
- Treatment failure: death due to uncontrolled infection or if patient showed a positive *M. chimaera* culture despite antimicrobial therapy for at least 3 months

Results
Population at risk and prevalence
From August 2008 to May 2012, a total of 3706 cardiovascular procedures with extracorporeal circulation were conducted.
- 6 disseminated *M. chimaera* cases were identified (0.16%)
- 4 additional cases (1 from Freiburg (DE), 2 from NL, and 1 pediatric case from Rotterdam (NL)

Patient characteristics
- 9 confirmed cases and 1 probable case (Table 1)

Manifestations of disease
- Fever, shortness of breath, fatigue, weight loss
- Splenomegaly, other physical findings unspecific
- In all patients anaemia: lymphocytopenia and thrombocytopenia
- In all patients: Elevated CRP, LDH, transaminases, and creatinine

Confirmed cases
Cardiac manifestations
Five cases with PVE, two with PVGI and one with myocarditis
Child: infection of prosthetic band and mycotic aneurism of pulmonary artery.

All diagnoses after cardiosurgical reintervention with culture or PCR.
Delayed diagnosis between index surgery and detection of *M. chimaera*: 21 months, range, 5-40

Extracardiac manifestations
Six of nine with extracardiac manifestations prior to cardiac m.: bone infections, cholestatic hepatitis, nephritis or blood stream infection.

Antimicrobial therapy
Targeted therapy with clarithromycin or azithromycin, rifabutin or rifampicin, ethambutol, plus/minus amikacin, or moxiflocacin.
Time course in Figure 2. Overview of antimicrobial drugs and susceptibilities in Table 2.
**Outcome**
At least eight patients with therapy failure according to our definition. Five patients died, four due to uncontrolled *M. chimaera* infection.

**Discussion**
- As of February 2015, 10 heart surgery patients form 4 hospitals in 3 different countries with disseminated *M. chimaera* infection.
- Source of infection: most probably airborne contamination during operation with *M. chimaera*
- Unspecific clinical manifestation after a very long incubation time
- Delayed diagnosis because mycobacterial culture is not part of routine diagnostic workup
- Outcome is very poor despite surgical reintervention and long-term antimicrobial therapy
- In 8 of 16 Swiss hospitals, 1 of 1 German hospital, and 8 of 8 Dutch hospitals, *M. chimaera* was found in the HCU
- Ongoing whole genome sequencing indicates a match between patient isolates and air samples
- For mycobacterial blood culture, the BacTec myco Lytic/F or the isolator tubes should be used multiple times on separate days
- *M. chimaera* isolates were uniformly susceptible to clarithromycin. A combination of clarithromycin, rifabutin, and ethambutol was used for basis of treatment

**Important implications:**
1. Inclusion of *M. chimaera* infection in differential diagnosis of patients with previous cardiac surgery and extracorporeal circulation.
2. HCUs are a potential source of *M. chimaera* and have to be identified and avoided. Recommendations for prevention of these infections are strongly warranted.
3. These infections are recalcitrant to classic therapy due to intrinsic antibiotic resilience, challenging infection sites (e.g. bone) and biofilm formation on implants.

15.9.2015 / DG