California Department of Public Health (CDPH)
Center for Health Care Quality
Healthcare-associated Infections (HAI) Program

# Mycobacterium chimaera Infections Associated with Exposure to Heater-Cooler Devices during Open Chest Cardiac Surgery

## Case Descriptions

Following are descriptions of the clinical presentations, diagnoses, treatments, and outcomes of *M. chimaera* cases in Switzerland, Germany, Netherlands, and U.S. derived from medical journals and public fora. The European cases are not mutually exclusive. Rather, serial publications described characteristics as more cases were identified. Please refer to the publications or online postings for more information and to see the tables and figures referenced.

**Achermann Y, et al., *Prosthetic valve endocarditis and bloodstream infection due to Mycobacterium chimaera.* J Clin Microbiol (51)6, 2013**

Patient 1

In June 2011, a 58-year-old male was admitted to the hospital for mitral and aortic valve replacement. In 2008, the patient had undergone aortic and mitral reconstruction with implantation of a mitral annuloplasty ring. Twelve months prior to the current admission, the patient experienced intermittent fever, weight loss, and respiratory distress. PVE was ruled out with repeated negative conventional blood cultures and a transesophageal echocardiogram that showed only moderate mitral and aortic insufficiency not suggestive of infective endocarditis. At that time, systemic sarcoidosis had been diagnosed based on unspecific granulomatous inflammation in liver and kidney biopsy specimens, a reticular pattern on the chest X-ray together with a severely constrained CO diffusion capacity, and a bronchoalveolar lavage showing a predominance of lymphocytes but only a slightly elevated CD4/CD8 quotient. A Mycobacterium genus PCR from the preserved liver and kidney biopsy specimens was performed retrospectively 1 year later and showed negative results. Cultures from the bronchoalveolar lavage were negative for mycobacteria. Prednisone was given at a maintenance dose of 20 mg per day. Because of fatigue and edema in the patient's legs, the prednisone dose was increased to 50mg in the interval. HIV testing (for HIV-1 and HIV-2) was negative. Despite immunosuppressive therapy with steroids, the general health condition of this patient deteriorated over the course of a year.

In May 2011, the patient was hospitalized due to respiratory distress. Several conventional blood cultures remained negative, but a transesophageal echocardiogram showed evidence of severe mitral and aortic valve insufficiency. Therefore, the patient was referred to our tertiary care hospital for repeat valve surgery. On admission, the physical examination revealed pulmonary wheezing, a pansystolic heart murmur, and a chronic pilonidal sinus infection. Laboratory tests showed an elevated C-reactive protein level, and the patient was started on amoxicillin-clavulanic acid, assuming an infected pilonidal sinus. During surgery, a fraying of the prosthetic ring of the mitral valve was found, and there was evidence of destruction of the mitral and aortic cusps. Both valves were replaced by new bioprostheses. The antimicrobial therapy was changed to vancomycin and piperacillin-tazobactam in the setting of ventilator associated pneumonia and intraoperative findings suggestive of infective endocarditis.

The histopathological examination of the fibrous valve tissue showed a partly necrotizing, acute and chronic inflammation with numerous foamy macrophages containing many periodic acid-Schiff- and acid-fast-positive bacteria, consistent with the diagnosis of an acute necrotizing mycobacterial endocarditis (Fig. 1). Further molecular analysis of the formalin fixed paraffin-embedded (FFPE) tissue

showed the presence of M. avium complex (MAC). Subsequent cultures of the prosthetic ring of the mitral valve annulus allowed identification of *M. chimaera* based upon the 16S rRNA gene sequence. A disseminated NTM infection was confirmed by the molecular detection of M. chimaera in the tracheal secretion and three consecutive heparin blood cultures. Despite targeted drug therapy with clarithromycin, rifabutin, and ethambutol (Table 1), the patient died 15 days later due to progressive heart failure. Permission for an autopsy could not be obtained.

Patient 2

A 51-year-old man was hospitalized in July 2011 with a 4-month history of fever of unknown origin accompanied by splenomegaly, progressive renal insufficiency, elevated liver enzyme levels, and pancytopenia. His medical history was remarkable for a previous herpes zoster infection, candida esophagitis, and the insertion of a composite graft (a mechanical aortal valve and prosthetic aortic arch) after an aortal dissection in January 2010. During hospitalization, PVE was ruled out with transesophageal echocardiography. *M. chimaera* was cultivated from bone marrow samples, two different blood cultures, one urine sample, and a tracheal swab, prompting the diagnosis of a disseminated *M.chimaera* infection. The lymphocyte and CD4 cell counts were 380 and 237 cells/l, respectively, suggesting a primary or secondary immune deficiency. A mutation in the interleukin 12 (IL-12)/interferon (IFN) pathway or an idiopathic CD4 lymphopenia was discussed as the underlying condition after an HIV infection had been excluded (by a screening antigen/antibody test, the HIV load, and a product-enhanced reverse transcriptase [PERT] assay). Targeted drug therapy with clarithromycin, rifabutin, and ethambutol was started at the end of August 2011 (Table 1).

In April 2012, the patient died suddenly due to splenic rupture as a consequence of a splenic infarction. Coincidentally, the ophthalmologist ascertained multiple chorioretinal spots of various ages consistent with arterial emboli. The necropsy of the heart, the mechanical valve, and the arterial graft did not show any signs of endocarditis or a vascular graft infection. The postmortem analysis of the spleen, liver, and kidneys revealed acute and chronic granulomatous inflammation with numerous macrophages containing many acid-fast-positive bacteria, consistent with the diagnosis of acute necrotizing mycobacterial disease. Molecular analysis of the formalin-fixed paraffin-embedded tissue identified the presence of and the arterial graft did not show any signs of endocarditis or a vascular graft infection. The postmortem analysis of the spleen, liver, and kidneys revealed acute and chronic granulomatous inflammation with numerous macrophages containing many acid-fast-positive bacteria, consistent with the diagnosis of acute necrotizing mycobacterial disease. Molecular analysis of the formalin-fixed paraffin-embedded tissue identified the presence of *M. chimaera* DNA in the spleen, the liver, and the kidney. In addition, *M. chimaera* was cultured postmortem from the patient's urine. Antimicrobial susceptibility testing (AST) showed that the strain was susceptible to clarithromycin (MIC, 4 mg/liter), according to the current NCCLS AST guidelines (4). Furthermore, the MICs of ethambutol and rifabutin were 5 mg/liter and 2 mg/ liter, respectively (Table 1). However, no clinical breakpoints for ethambutol, rifampin, and slow-growing nontuberculous mycobacteria currently exist.

**Sax H, et al., *Prolonged Outbreak of Mycobacterium chimaera Infection After Open-Chest Heart Surgery.* Clin Infect Dis (61)1, 2015**

A total of 6 male patients with *M. chimaera* met our case definition. Patient characteristics are shown in Table 1. All had undergone open-chest heart surgery involving implants at the University Hospital of Zurich between 2008 and 2012. Latency between surgery and manifest infection ranged between 1.5 and 3.6 years (Figure 1). In all cases except 1 patient with sustained *M. chimaera* bacteremia, the cardiac implant showed echocardiographic signs of endocarditis. Accompanying symptoms, signs, and disorders were fatigue, fever, hepatitis, renal insufficiency, splenomegaly, and pancytopenia. Host defense was compromised in 2 patients. One patient had lowered CD4 cell counts for no obvious reason, and 1 had

received steroid medication for a supposed granulomatous autoimmune disease. As prosthetic valves and aortic grafts differed in type, manufacturer, and lot, a production-related contamination cause appeared highly unlikely (Table 1). No potential common exposure sources outside the hospital could be identified among patients. RAPD-PCR analysis of isolates of the 6 cases repeatedly revealed 2 clusters with similar patterns involving 2 patients and 3 patients each (Figure 2). The isolate of 1 patient had a unique RAPD-PCR pattern."

Targeted antibiotic therapy consisted of a prolonged combination of clarithromycin, rifabutin, and ethambutol, combined with either amikacin or moxifloxacin. Three patients experienced breakthrough infections with splenic embolus, pacemaker pocket infection, and progressive mitral valve endocarditis, respectively. Three patients underwent valve replacement surgery; 1 patient required repeated surgical debridement. Two other patients died, despite antibiotic treatment [11].

**Kohler P, et al., *Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated Mycobacterium chimaera infections subsequent to open heart surgery*. Eur Heart J (36)40, 2015**

Patient characteristics

Overall, nine confirmed cases including eight adults and one child, and one probable case are described. For the adult patients the median age and median BMI were 61 years (range, 36–76) and 24.9 kg/m2 (23.4–35.7), respectively. Details on the index cardiac surgery are shown in Table 1. The median extracorporeal circulation time was 191 min (range, 123–294). Two patients had diabetes mellitus, one patient received azathioprine and salazopyrine for Crohn's disease, and one patient had lymphocytopenia of unknown origin. After the index surgery, two patients received corticosteroid treatment for presumptive sarcoidosis and one patient received repetitive intra-articular methotrexate for suspected rheumatologic disease. All patients were HIV negative. The child with a congenital cardiac anomaly was in neonatal age when he received a correction of the aortic anomalies and banding of the pulmonary artery.

Manifestations of disease

The most common initial complaints in adults were fever, shortness of breath, fatigue, and weight loss. Physical findings were nonspecific with the exception of splenomegaly. All patients had anaemia, pronounced lymphocytopenia, and thrombocytopenia. C-reactive protein, lactate dehydrogenase, transaminases, and creatinine levels were elevated in all subjects. In the infant, clinical suspicion arose due to fever episodes and failure to thrive.

Cardiac manifestations in confirmed cases

Five of the nine patients with confirmed diagnosis presented with PVE, two with PVGI and one with myocarditis. The child presented with infection of the prosthetic band and a mycotic aneurysm of the pulmonary artery. All diagnoses were made upon cardiosurgical reintervention with cultures or PCR from cardiac tissue being positive for *M. chimaera*. No other microorganisms were detected in the blood, and there was no serological evidence of a culture-negative endocarditis of other cause (i.e. Bartonella spp., Brucella spp., Coxiella burnettii, Tropheryma whipplei). Diagnosis was delayed with a median duration between index surgery and culture confirmed diagnosis of almost 2 years (21 months; range, 5–40). Affected patients presented with prevailing cardiac complications like severe valve insufficiency and subsequent reduction in ejection fraction, paravalvular abscess, or pseudoaneurysm formation (Figure 1). The TEE showed paravalvular regurgitation or leakage, anteroseptal pseudoaneurysm as well as a paravalvular abscess with extension into the interatrial septum (Figure 1A). Additionally, vegetations or multiple short, thin and sparse filaments on the ventricular side were detected (Figure 1B)."

Extracardiac manifestations in confirmed cases

In six of nine patients with confirmed diagnosis, extracardiac manifestations preceded cardiac disease. Among the first disease manifestations were bone infections (osteoarthritis, spondylodiscitis, or sternal wound infection together with a large retrosternal abscess formation), cholestatic hepatitis, nephritis, or blood stream infection. Mycobacterial blood cultures were positive a priori in four patients. At the time of diagnosis, most patients had splenomegaly. In the course of the disease, patients developed bi- or even pancytopenia, panuveitis, or multifocal chorioretinitis (Figure 1H), pneumonitis (Figure 1E) or cerebral vasculitis. One patient developed a surgical site infection with *M. chimaera* at the removal site of the saphenal vein."

Probable case

The probable case (Table 1, Patient 9) presented with fever of unknown origin subsequent to open heart surgery. He had been treated for presumptive sarcoidosis due to granulomatous hepatitis, but persistent fever prompted new diagnostic procedures including a PET/CT scan. Diagnosis of *M. chimaera* infection was ascertained after biopsy of the right sternoclavicular joint, bone marrow, liver, and blood cultures. However, TEE did not reveal any signs of endocarditis.

Antimicrobial therapy

The detailed time course of events and treatment information is depicted in Figure 2. Targeted antimicrobial therapy consisted of clarithromycin or azithromycin, rifabutin or rifampicin, ethambutol, plus/minus amikacin, or moxifloxacin. The number of available analyses, mean drug doses, serum maximum observed concentration levels, and the percentage of analyses revealing subtherapeutic drug concentrations are recorded in Supplementary material online, Table S3. In more than half of the cases the recommended macrolide drug levels were not reached. The same holds true for rifabutin, ethambutol, moxifloxacin, and amikacin. Antimicrobial drugs, tested drug concentrations, and phenotypic drug susceptibilities of patient isolates are provided in Table 2. Drug susceptibility testing of breakthrough isolates was unchanged.

Outcome

At least eight patients experienced therapy failure according to our definition. Five patients died, four of them due to uncontrolled *M. chimaera* infection despite being under targeted combination therapy for 15, 31, 270, and 375 days, respectively. Tissue cultures from Patient 3 (bone and annuloplasty ring (Figure 1G)), Patient 4 (sternoclavicular mass, epicardial pacemaker wire), Patient 8 (annuloplasty ring) and blood cultures from Patients 6 and 9 became positive for *M. chimaera* despite prolonged antimicrobial therapy (median 8 months, range 0.5–12). Persistent signs of infection (Patients 4 and 5, Figure 1C and D) and progressive chorioretinal lesions (Patient 5, Figure 1H) represented an indication for immediate cardiosurgical reintervention. Of note, all these patients were previously considered inoperable due to presumptively high perioperative mortality, but the risk to benefit assessment changed in the light of uncontrolled *M. chimaera* infection. Currently, three patients are in a post-treatment monitoring period."

**Haller S, et.al., *Contamination during production of heater-cooler units by Mycobacterium chimaera potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016.* Euro Surveill (21)17, 2016**

At the beginning of our investigation, in April 2015, we were informed by cardiac surgery centre A in Germany about a confirmed case that became symptomatic before 2015 [3]. During April 2015 to February 2016, the mandatory surveillance of healthcare-associated outbreaks identified four additional confirmed cases of *M. chimaera* infection who had been exposed to an HCU (heater-cooler unit) in two different cardiac surgery centres (B and C) in Germany (Table 1). These cases developed a symptomatic

*M. chimaera* infection five months to five years after exposure to a HCU. All five confirmed cases were male and aged above 50 years (range 53–80) when diagnosed with *M. chimaera* infection, four had aortic valve replacement and two underwent coronary artery bypass grafting, one died. All had been exposed to HCUs from one single manufacturer during open chest surgery. No cases with NTM infections other than *M. chimaera* were notified. Our investigations did not reveal epidemiological links between cases of the different sites.

**Miller J, Pennsylvania Department of Public Health, FDA Advisory Committee Meeting Transcript, June 2, 2016**
***(http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM509590.pdf)***

Four patients with heater-cooler exposure greater than 5 hours, on-pump time greater than 2 hours, with implants, had…a remarkable constellation of isolates… they have blood, they have spleen, they have bone marrow. And for you clinicians in the room, you may be thinking, bone marrow? Well, in fact, these patients early on…may be presenting with very nonspecific findings. And so a number of these had pancytopenias and were worked up for malignancies. And so they had a bone marrow biopsy, and they were found to have granulomatous disease.

One patient had a deep abscess… exposure [to] heater-cooler unit, greater than 5 hours, on pump for less than 2 hours, also had an implant.

One patient had "deep sternal wound. It was actually vertebral osteomyelitis with an adjoining psoas abscess. So this patient…may have had vertebral osteomyelitis in an adjoining psoas abscess due to hematogenous spread…[an] indication of disseminated infection.

**Diekema D, University of Iowa Hospitals and Clinics, FDA Advisory Committee Meeting Transcript, June 3, 2016**
***(http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM509593.pdf)***

The first patient that we identified, a 59-year-old male who had aortic valve replacement on October of 2012 for a dilated aortic root and symptomatic aortic insufficiency that was performed at our university. This patient's care, all of the care delivery except for the surgery, was at another healthcare system because he lived more than 2 hours away from Iowa City. So he did well until about 15 months after the surgery, when he began to have back/chest pain, shortness of breath, cough, fever, pancytopenia, elevated transaminases, and weight loss. He had a very extensive ID evaluation, including multiple sets of blood cultures that were unrevealing. In April of 2014, he had a really profoundly positive clinical response to prednisone with near resolution of his symptoms. He was provisionally diagnosed with sarcoidosis. I think we've heard that here before. But when his symptoms began to recur after the prednisone course was completed, further workup for a malignancy with the bone marrow and a BAL for further evaluation for sarcoidosis. In both of those procedures in this healthcare system, AFB cultures are standard. They're just done whenever they receive these samples. They both grew M. chimaera. Not knowing exactly what to make of that finding, this patient found his way back to a local infectious disease provider who did blood cultures which also grew *M. chimaera*; was then begun on multi-drug therapy and was never able to really clear his mycobacteremia, had positive, monthly positive blood cultures due to *M. chimaera*.

So how did we learn about the case? Well, January 19th of this year, our infectious disease on-call physician received a call from the local ID provider requesting assistance with a clinical syndrome he'd not seen before: an intractable, invasive, disseminated *M. chimaera* infection. We noted that the patient

had had bypass surgery for this aortic valve replacement at our institution. We were aware by the time of the situation and the elegant work of Dr. Sax and his colleagues and the experience in Pennsylvania that you've already heard about. So we felt that since there were no other obvious exposures or risk factors for this patient's infection, we absolutely had to initiate an outbreak investigation."

The second case had been referred from a local provider for a systemic granulomatous inflammatory process, liver and bone marrow biopsies showing non-caseating granulomas, but all the micro-stains negative. And our hepatologist heard our presentation on this and immediately recognized that this patient was at risk and ordered AFB blood cultures.

Case 3 was being followed at our institution for a very complicated course after -- before and after cardiac transplant, had just not been doing well on a number of fronts, and the transplant cardiology and transplant ID coordinated AFB blood cultures.

So this is…a summary of the three cases at our institution that we have identified to date. Just some common features…. All had some kind of prosthetic material in place: Case 1, an aortic valve; Case 2, an aortic arch graft; Case 3 had had three VAD procedures and a heart transplant and during the process also had an aortic arch repair performed and graft material in place…. All have invasive disease, positive blood cultures. The time to symptom onset was over a year in all cases. It's a little unclear in Case 3 because the exposures occurred over the course of 11- 13 months. The time to diagnosis, over 3 years or close to 3 years in all cases. The first case unfortunately died in May of this year as a direct result of this infection. The other two are under treatment in an extremely complicated clinical scenario.