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?

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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[a]; Institute of Clinical Pathology, University and University Hospital Zurich, Zurich, Switzerland[b]; Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland[c]; Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland[d]

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.

Journal of Clinical Microbiology p. 1769–1773 June 2013 Volume 51 Number 6

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…

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granulocytic demarcation

necrotic value tissue

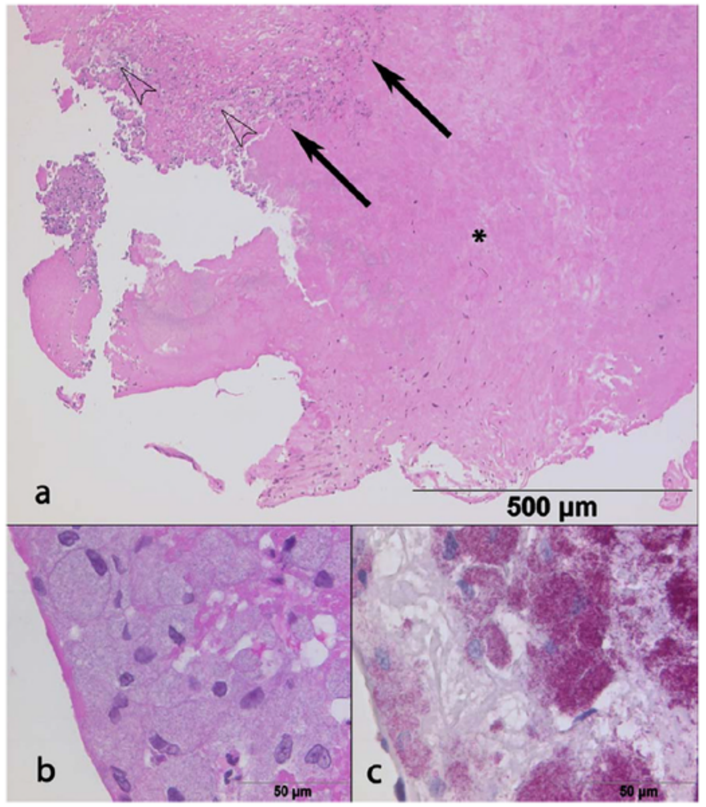

FIG 1 Histopathological analysis of valve tissue from patient 1. (a) Overview of the necrotic valve tissue (*) with granulocytic demarcation (arrows) and foamy macrophages (arrowheads) (hematoxylin and eosin [H&E] stain); (b) swollen foamy macrophages (H&E stain); (c) presence of numerous acid-fast bacilli (Ziehl-Neelsen stain).

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

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Randomly amplified polymorphic DNA

(primers according *M. abscesses*)

No other matching strains found in hospital

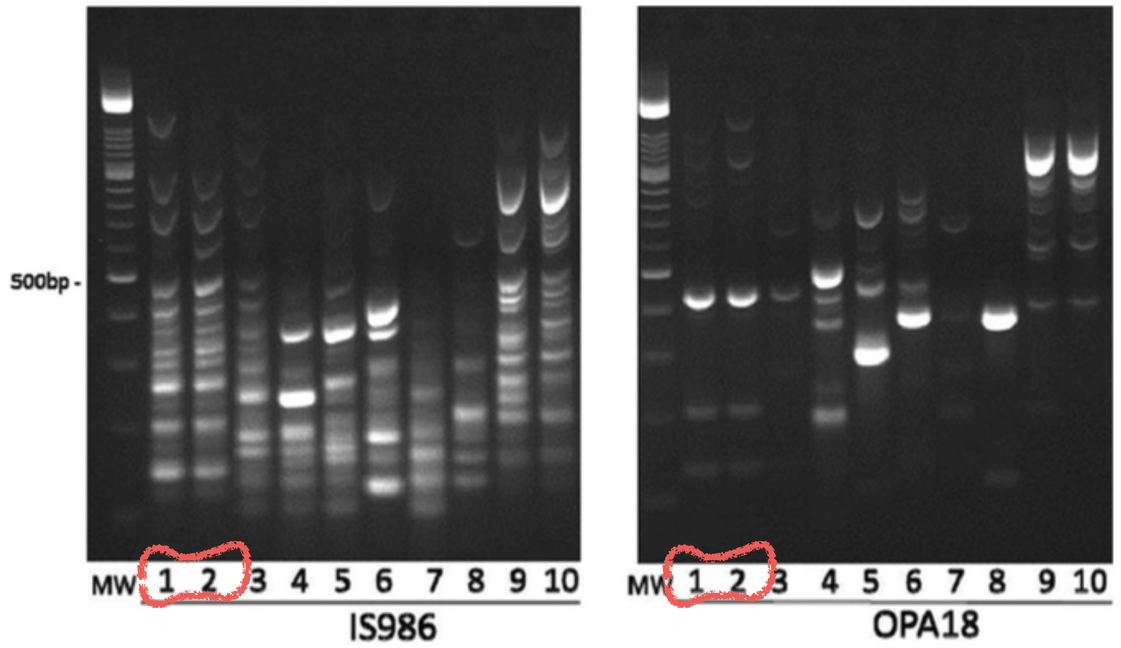
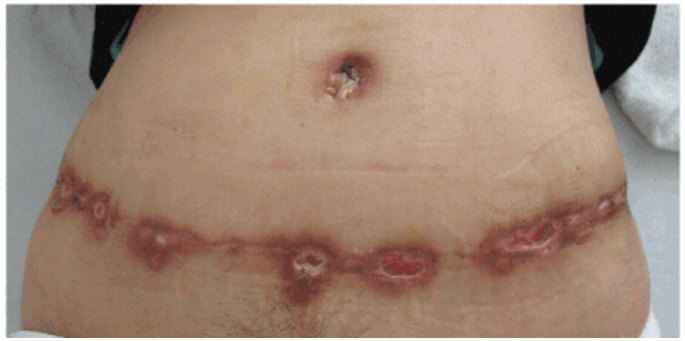
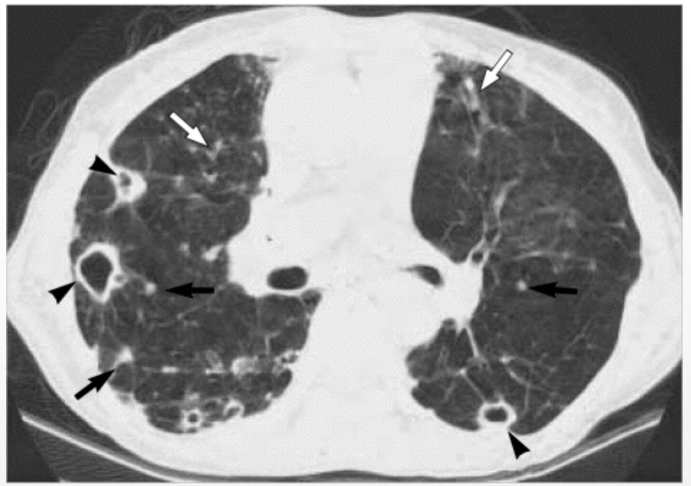


FIG 2 *Mycobacterium chimaera* strain typing using randomly amplified polymorphic DNA (RAPD)-PCR. Shown are RAPD-PCR patterns of *M. chimaera* clinical isolates from the two patients (lane 1, patient 1; lane 2, patient 2) and of eight respiratory culture isolates from eight different patients (lanes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





Surgical site infection with non-tuberculous mycobacteria

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Outbreak investigation from 2013

Sax H, Bloemberg G, Hasse B, Sommerstein R, Kohler P, Achermann Y, Rössle M, Falk V, Kuster SP, Böttger EC, Weber R. **Prolonged outbreak of Mycobacterium chimaera infection after open chest heart surgery.** Clin Infect Dis 2015;61(1):67-75

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Observations

Video analysis

Interviews

Workflow analysis

Mycobacteria cultures

Patient heating blanket water circuit

Heater-cooler unit water tanks/circuits

Showers

Drinking water fountains

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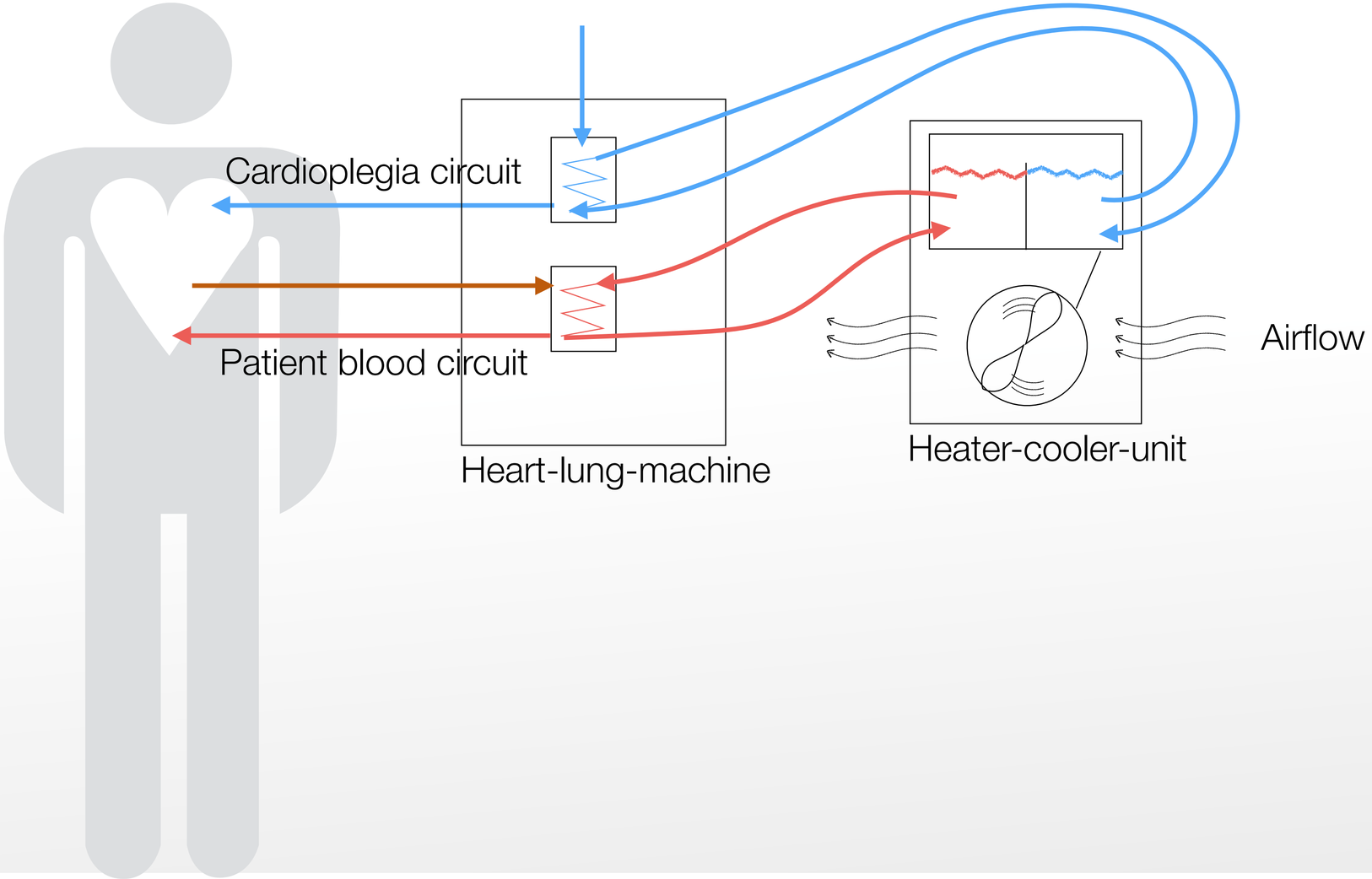
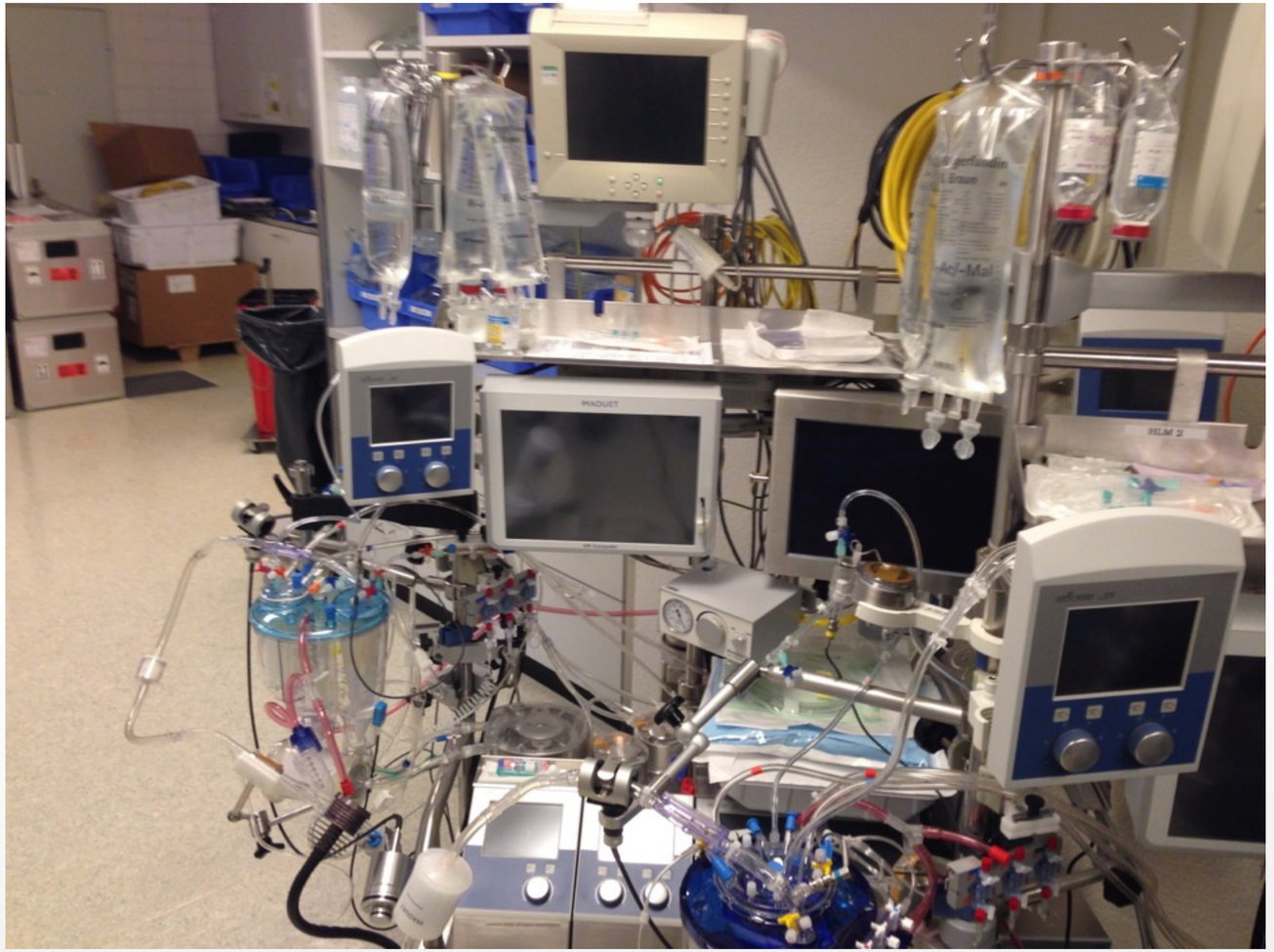

Cardioplegia circuit
Patient blood circuit
Heart-lung-machine
Heater-cooler-unit
Airflow



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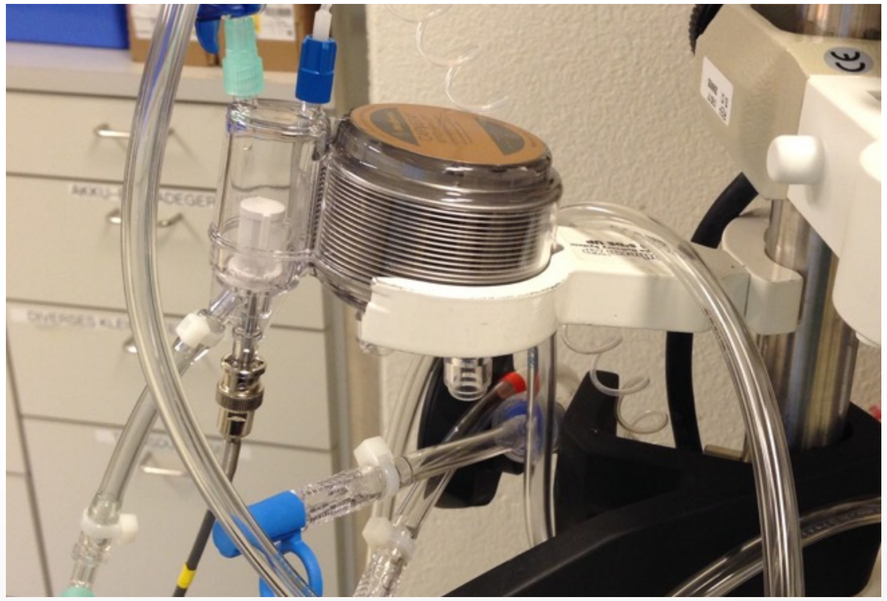
Heat-exchangers

Cardioplegia solution



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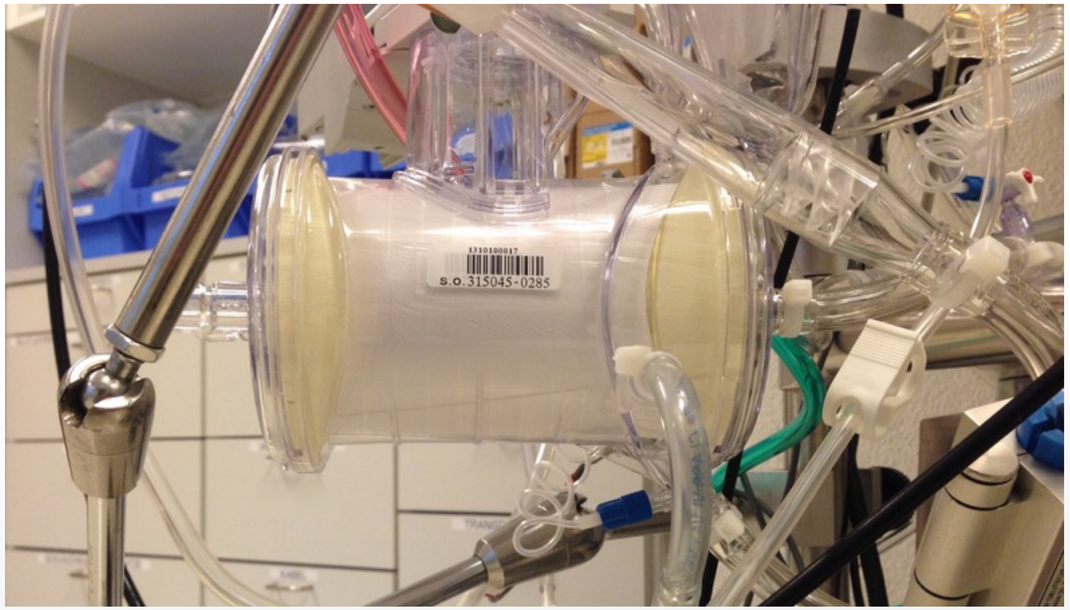

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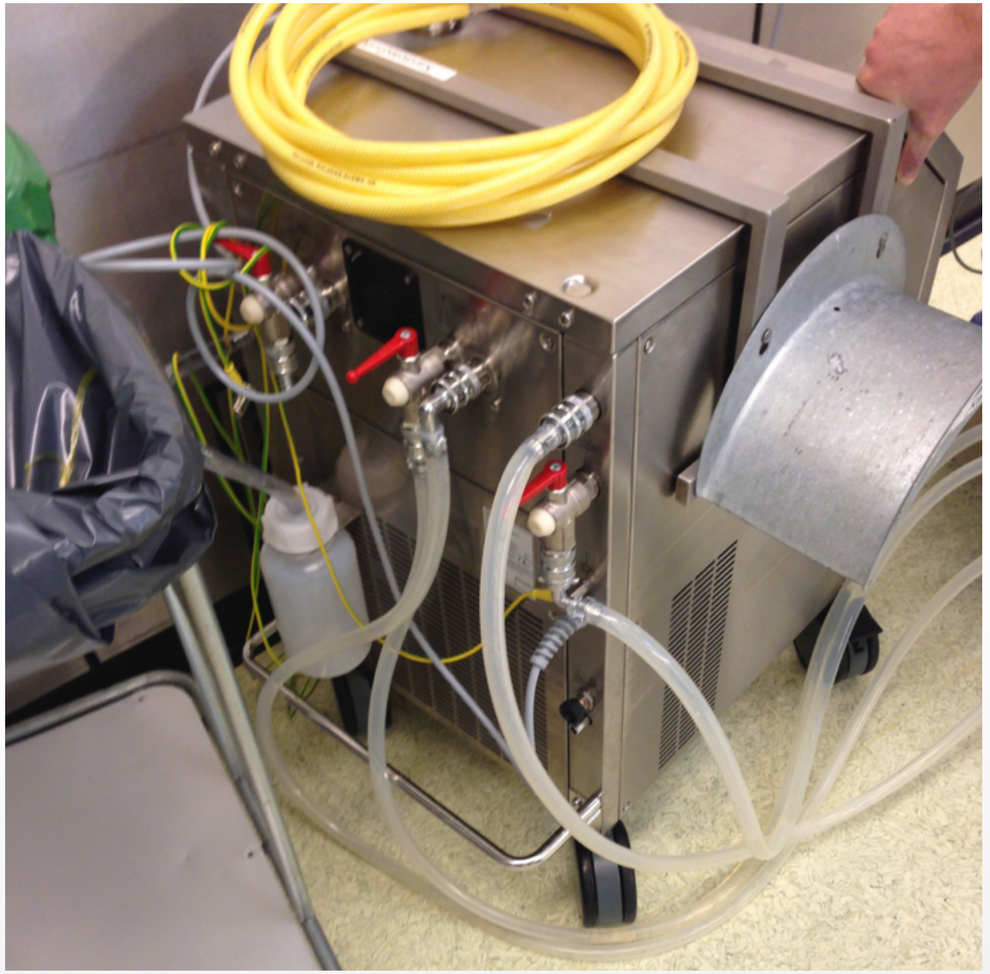

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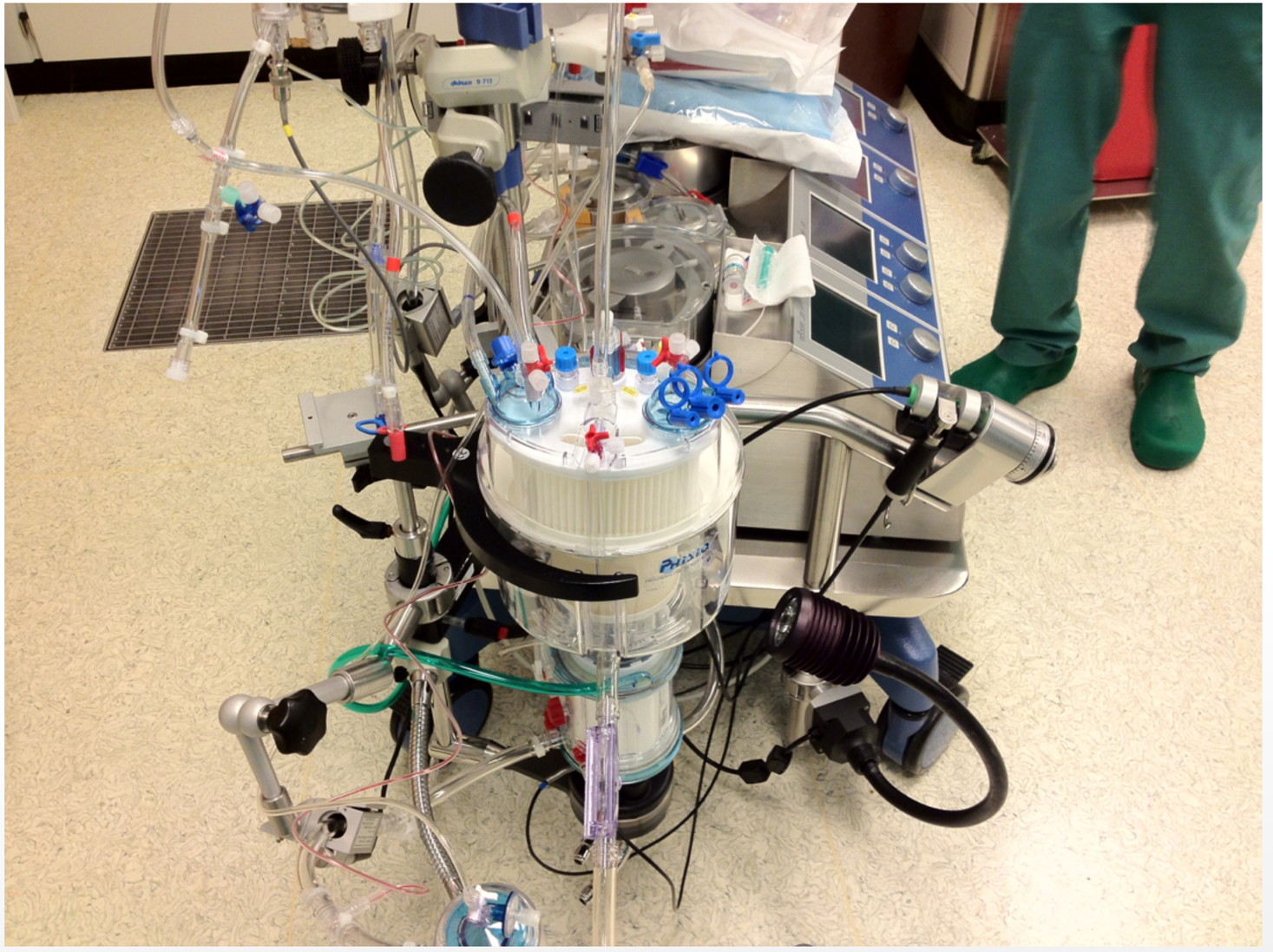

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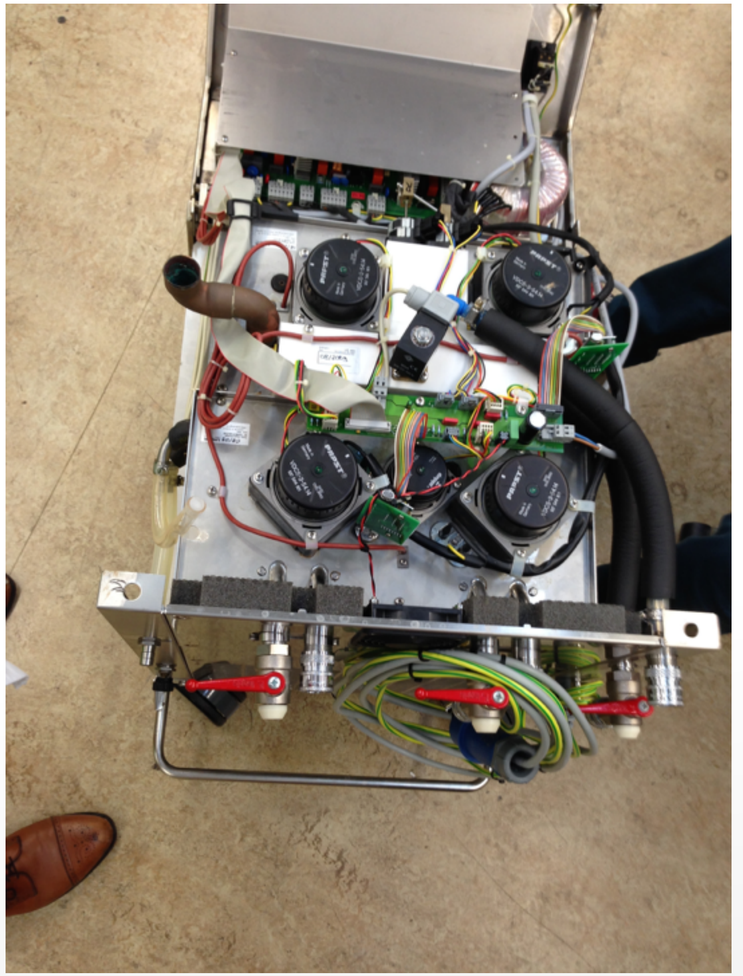
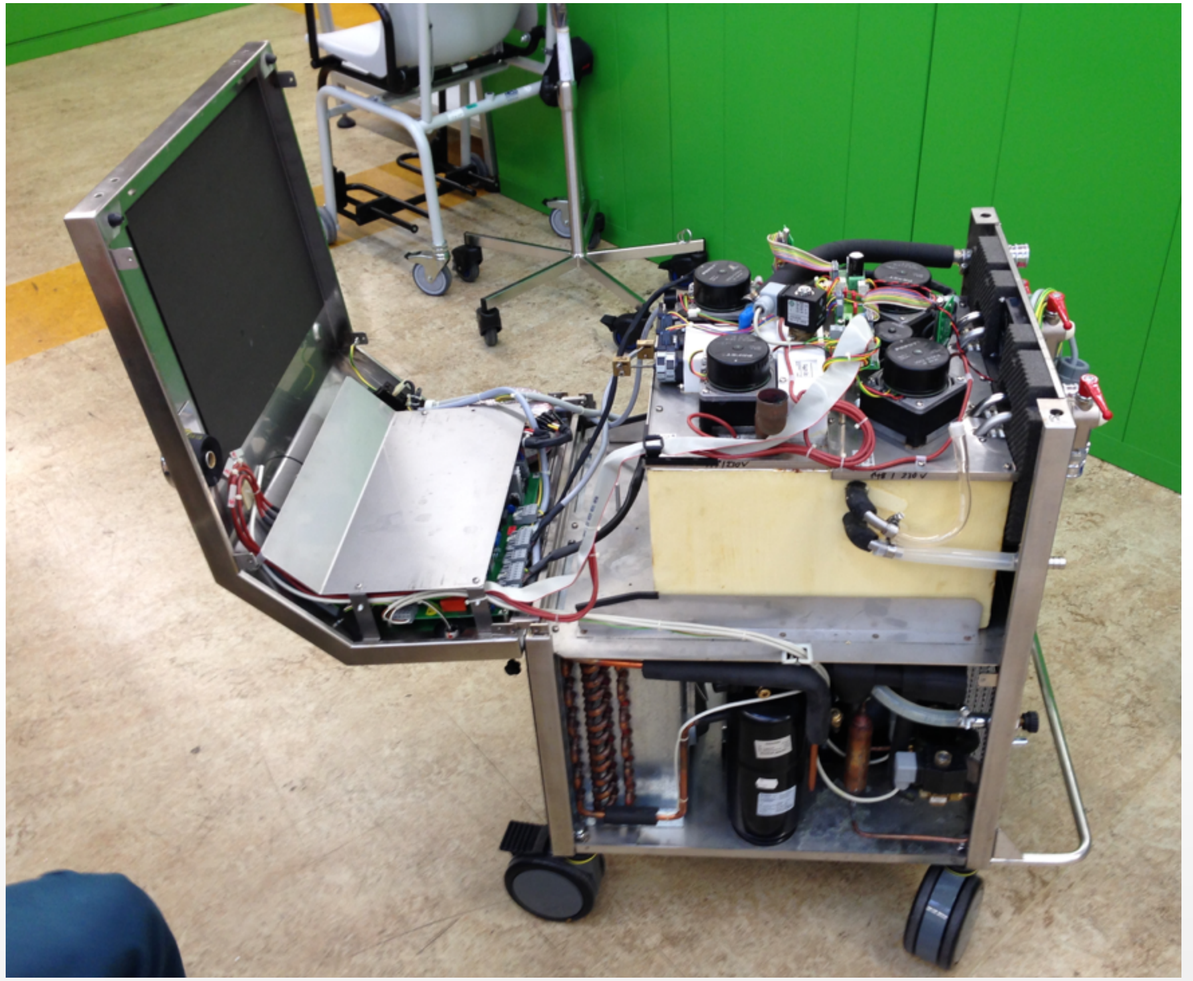
Ri-Ac/-M
B BRAUN





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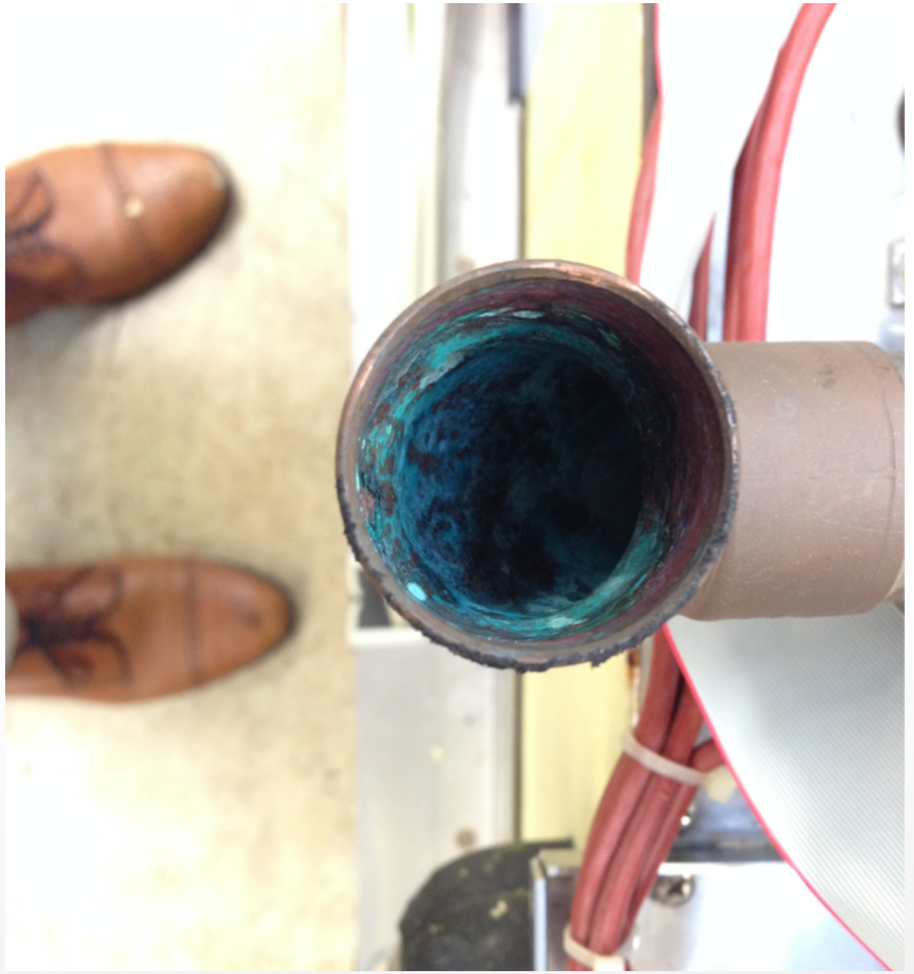

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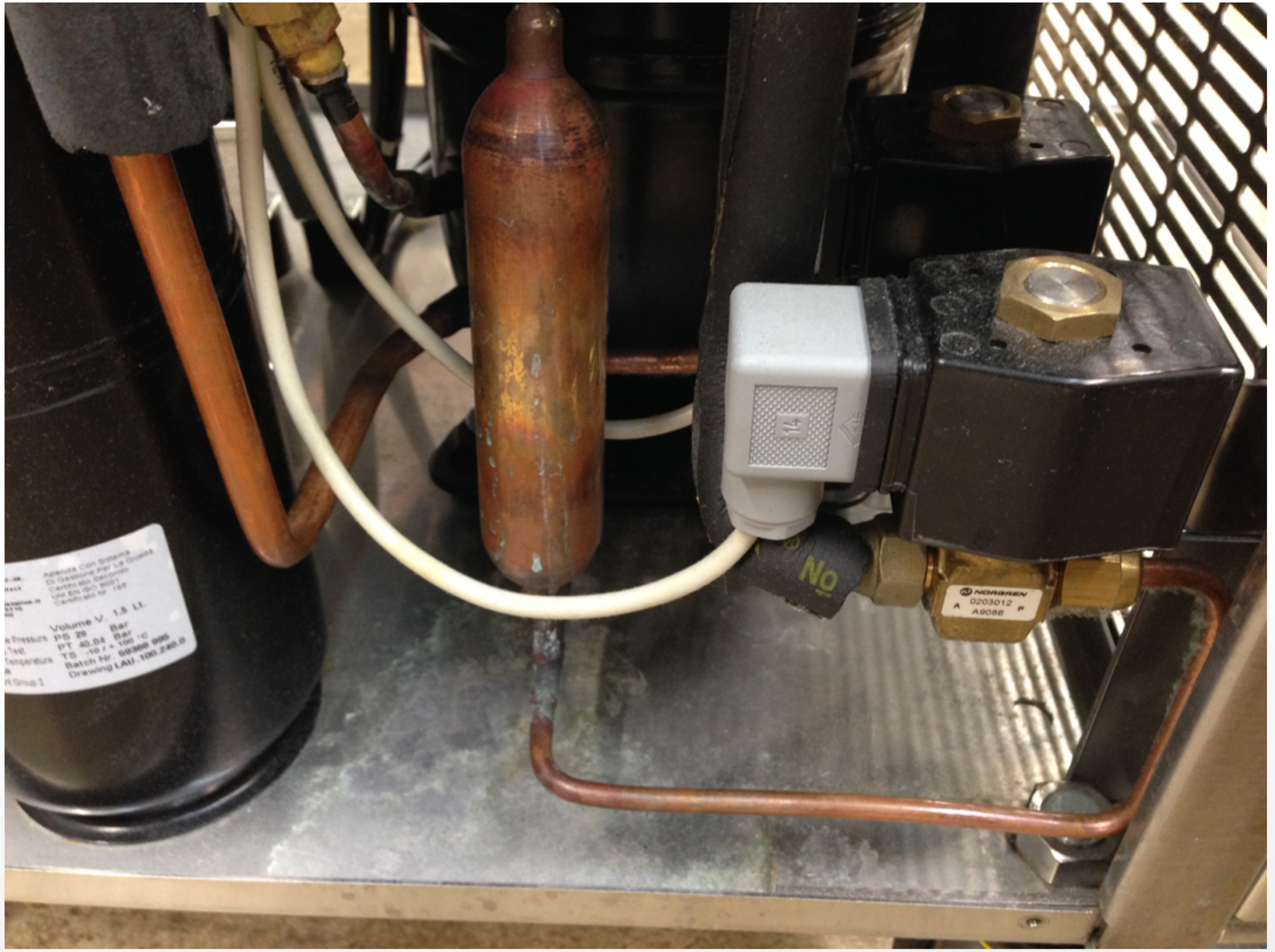
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Air cultures with heater-cooler unit turned ON

Air cultures with heater-cooler unit turned OFF

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Air cultures with heater-cooler unit turned ON

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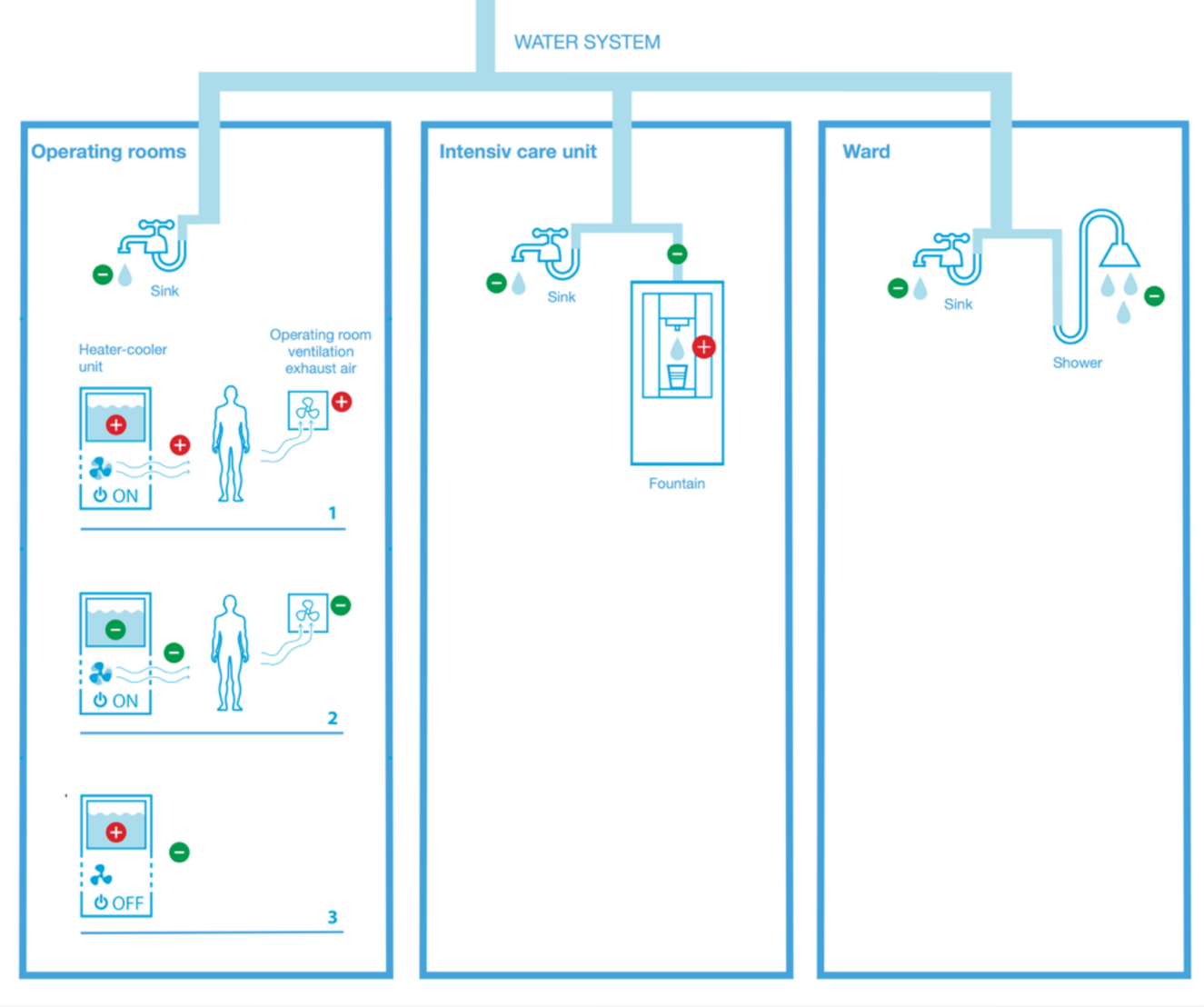

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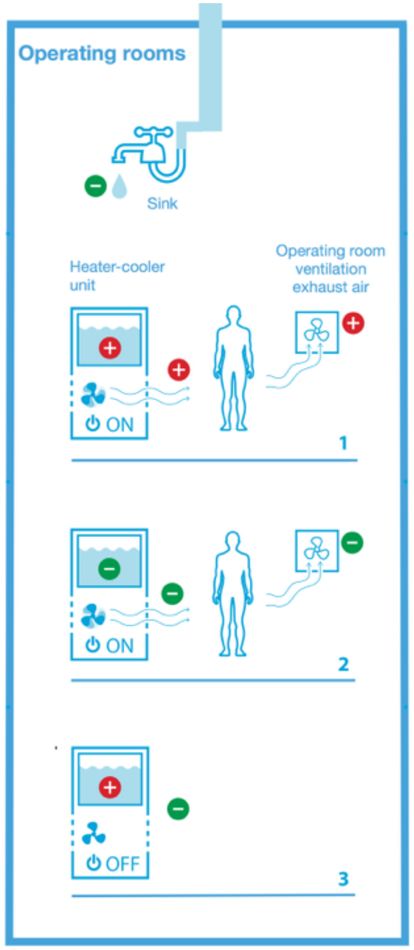
In the operating theatre

contaminated, ON

not contaminated, ON

contaminated, OFF



Air cultures → positive

Air cultures → negative

Air cultures → negative

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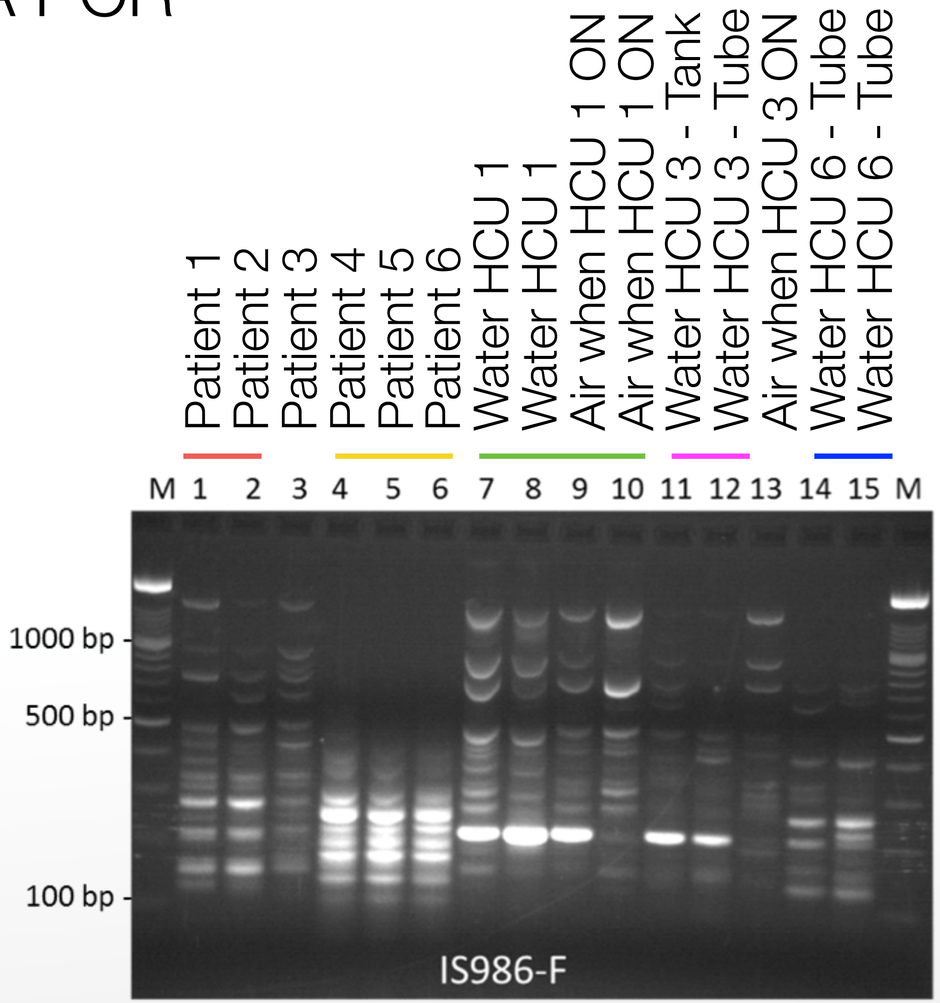
Randomly amplified polymorphic DNA PCR (RAPD-PCR)



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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.

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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.

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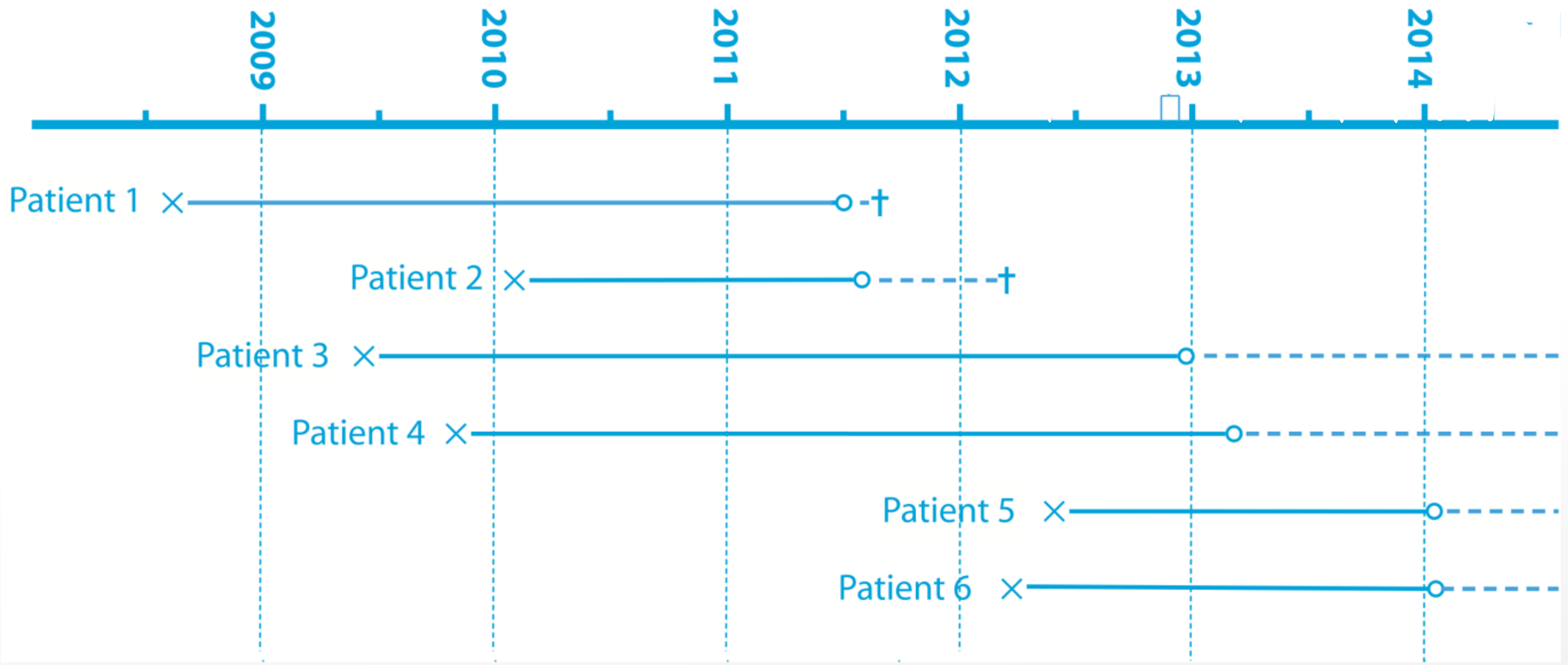
Patients with *M. chimaera* infection in Zurich, Switzerland



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Patient 2 †	51	2010	1.5	Composite graft for aortic dissection	25 mm ATS composite graft 8 mm GAHE Gelweave x prosthesis	Heart valve: pyrolytic carbon; Graft: double woven velour; Hemiarch: woven polyester	Bloodstream infection, splenomegaly, pancytopenia, hepatitis, pulmonary, ocular emboli	Blood, sputum, bone marrow, urine	Granulomatous myocarditis, pneumonitis, nephritis involvement of spleen
Patient 3	64	2009	3.6	Mitral valve reconstruction	32 mm x 2 mm Carpentier ring	Layers of Elgiloy Sewing ring with layers of silicone covered by polyester knit fabric	Endocarditis, wrist arthritis, pancytopenia, splenomegaly, hepatitis, renal Impairment, ocular emboli	Cardiac tissue and prosthesis, bone (wrist)	Granulomatous endocarditis osteomyelitis
Patient 4	49	2009	3.4	Aortic valve replacement	24 mm ATS Open Pivot AP Series Heart Valve	Heart valve: pyrolytic carbon; graft: double woven velour	Endocarditis, pancytopenia, splenomegaly, hepatitis, ocular emboli, pacemaker pocket infection	Cardiac tissue and prosthesis, deep tissue samples of pacemaker pocket	Granulomatous hepatitis, myositis
Patient 5	61	2012	1.7	Aortic root and arch replacement	ATS AVG 26 mm graft as elephant trunk	Valve: pyrolytic carbon; Hemashield Woven Double Velour Graft; Elephant trunc: collagen coated external velour polyester graft	Vascular graft infection, Bone (vertebral and sternal osteomyelitis) Splenomegaly Ocular emboli	Vertebral bone	Granulomatous osteomyelitis
Patient 6	63	2012	1.8	Aortic root and arch replacement	Medtronic Freestyle Aortic Valve 26x8mm, 50 cm Vascutek 10 mm Gelweave D: 10 mm, L: 15 cm	Biological Polyester	Vascular graft infection, splenomegaly, hepatitis, renal failure, multifocal chorioiditis	Cardiac tissue and prosthesis	Granulomatous interstitial nephritis

2008 - 2014

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 additional patient at that time

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July 14, 2014

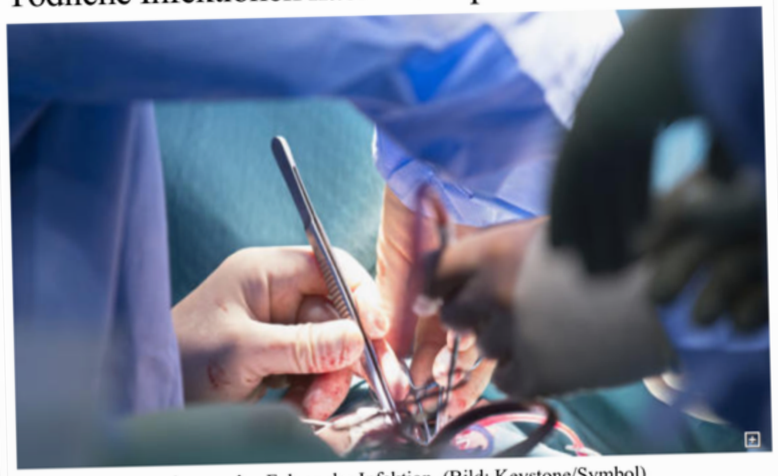
Tödliche Infektionen: Zürcher Unispital entdeckt Bakterium

Dienstag, 15. Juli 2014, 19:04 Uhr, aktualisiert um 19:56 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.

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

Tödliche Infektionen nach Herzoperationen



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

Bei Eingriffen am offenen Herzen in der Schweiz ist es zu vereinzelten Infektionen mit einem an sich harmlosen Bakterium gekommen. Vermutliche Quelle ist ein technisches Gerät, das bei den Operationen benutzt wird. In den Spitälern wurden Gegenmassnahmen getroffen.

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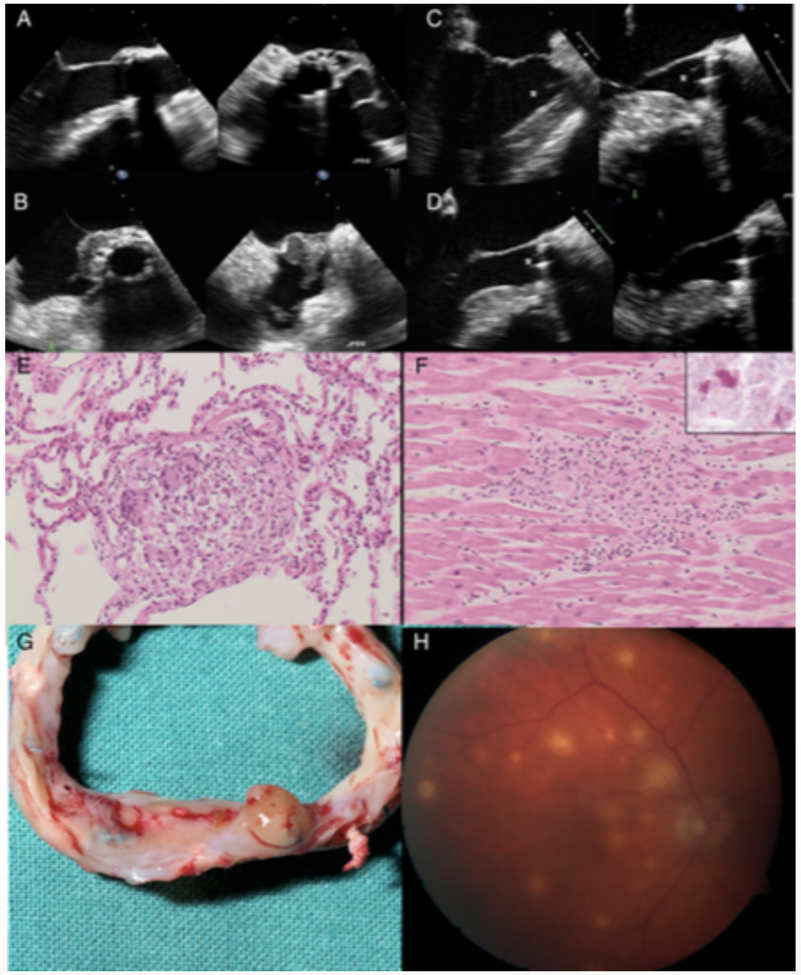
European Heart Journal
doi:10.1093/eurheartj/ehv342

FASTTRACK CLINICAL RESEARCH
Cardiovascular surgery

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

Philipp Kohler[1], Stefan P. Kuster[1], Guido Bloemberg[2], Bettina Schulthess[2,3], Michelle Frank[4], Felix C. Tanner[4], Matthias Rössle[5], Christian Böni[6], Volkmar Falk[7,8], Markus J. Wilhelm[7], Rami Sommerstein[1], Yvonne Achermann[1], Jaap ten Oever[9], Sylvia B. Debast[10], Maurice J.H.M. Wolfhagen[10], George. J. Brandon Bravo Bruinsma[11], Margreet C. Vos[12], Ad Bogers[13], Annerose Serr[14], Friedhelm Beyersdorf[15], Hugo Sax[1], Erik C. Böttger[2,3], Rainer Weber[1], Jakko van Ingen[16†], Dirk Wagner[17†], and Barbara Hasse[1†*]



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

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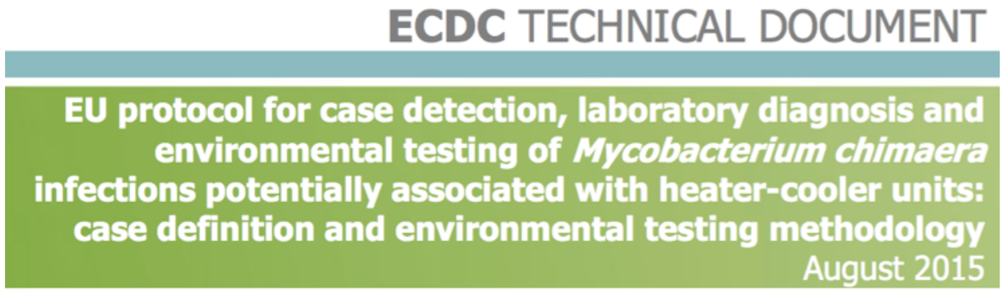

European Centre for Disease Prevention and Control. EU protocol for case detection, laboratory diagnosis and environmental testing of *Mycobacterium chimaera* infections potentially associated with heater-cooler units: case definition and environmental testing methodology. Stockholm: ECDC; 2015

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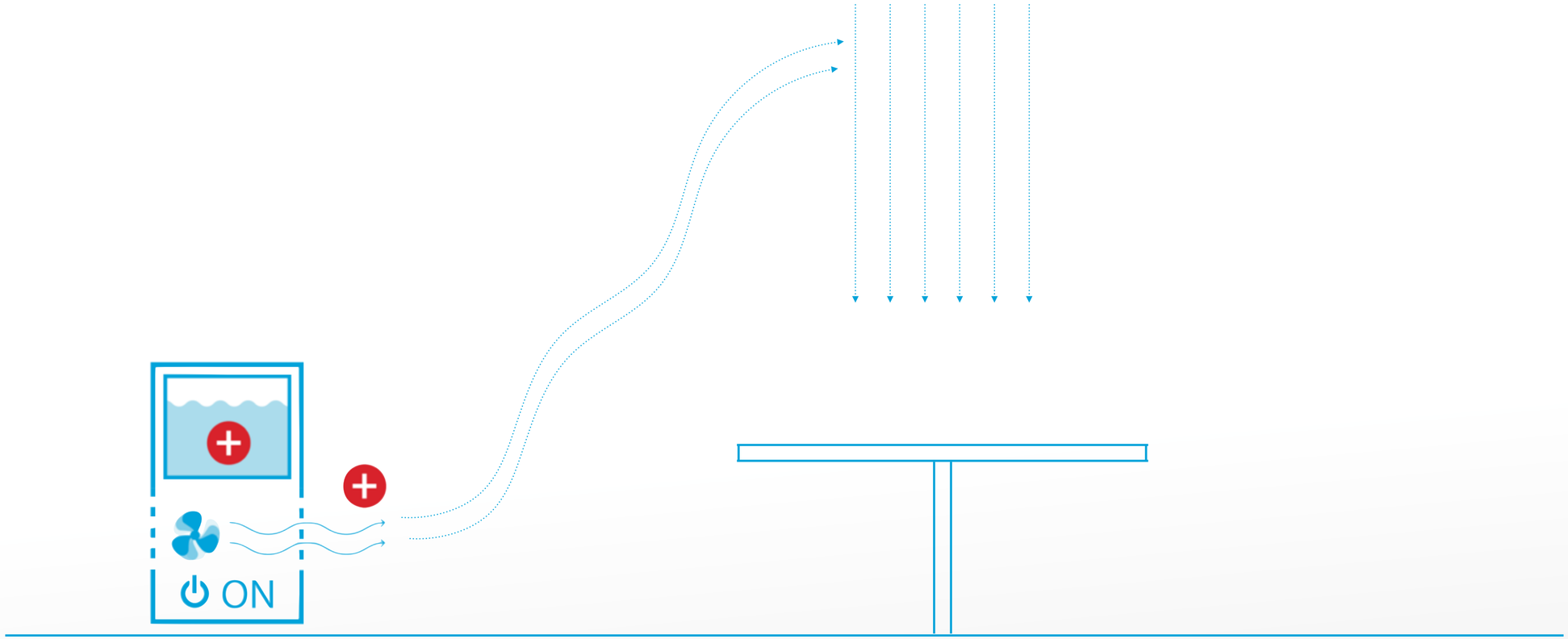

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Experience with cases

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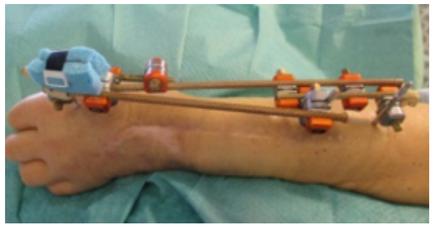
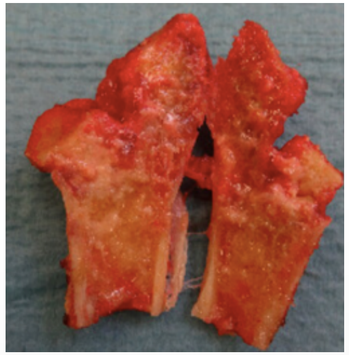

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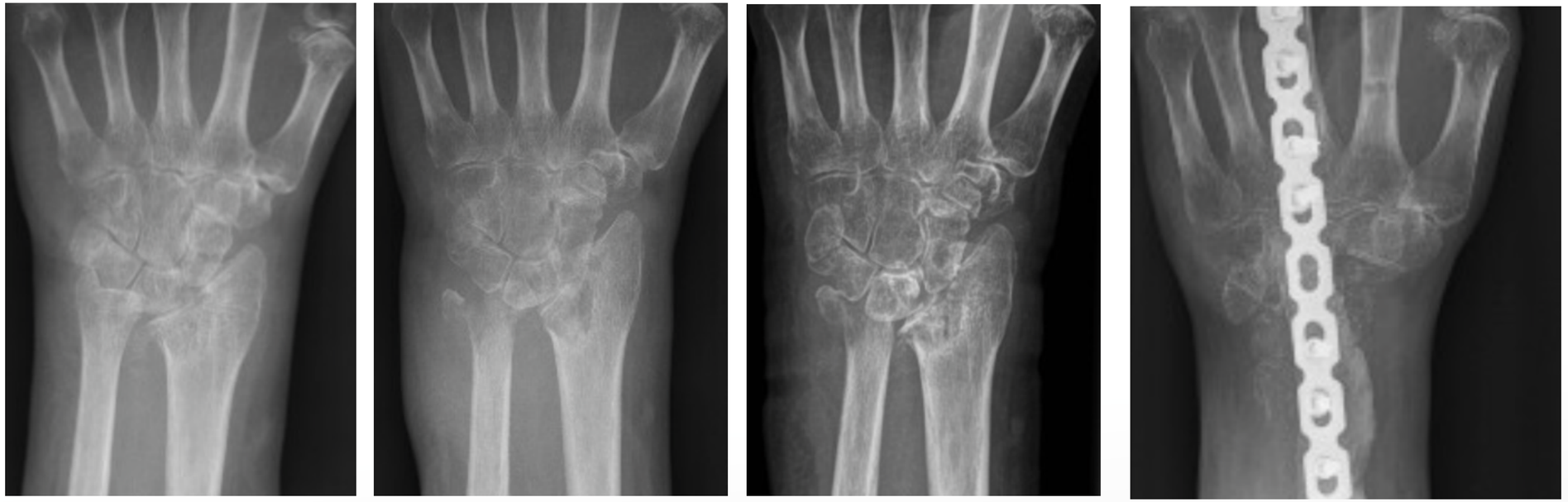

Biopsy cultures test negative after 9 months under AB Rx and multiple debridements

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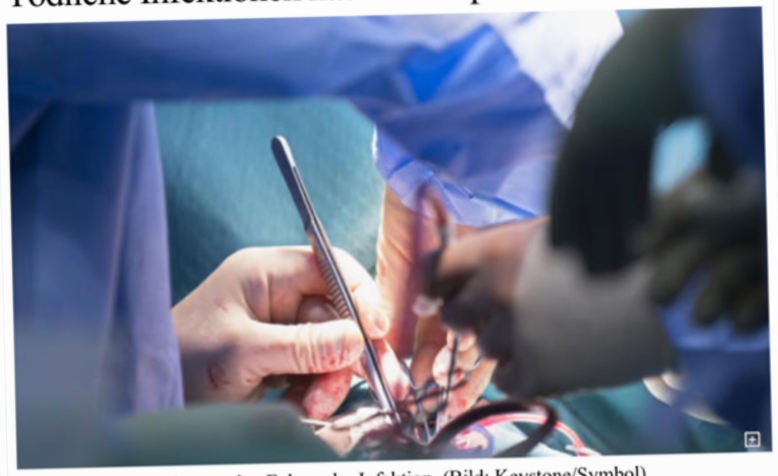

Zwei Patienten starben an den Folgen der Infektion. (Bild: Keystone/Symbol)

Bei Eingriffen am offenen Herzen in der Schweiz ist es zu vereinzelten Infektionen mit einem an sich harmlosen Bakterium gekommen. Vermutliche Quelle ist ein technisches Gerät, das bei den Operationen benutzt wird. In den Spitälern wurden Gegenmassnahmen getroffen.

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FASTTRACK CLINICAL RESEARCH
Cardiovascular surgery

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

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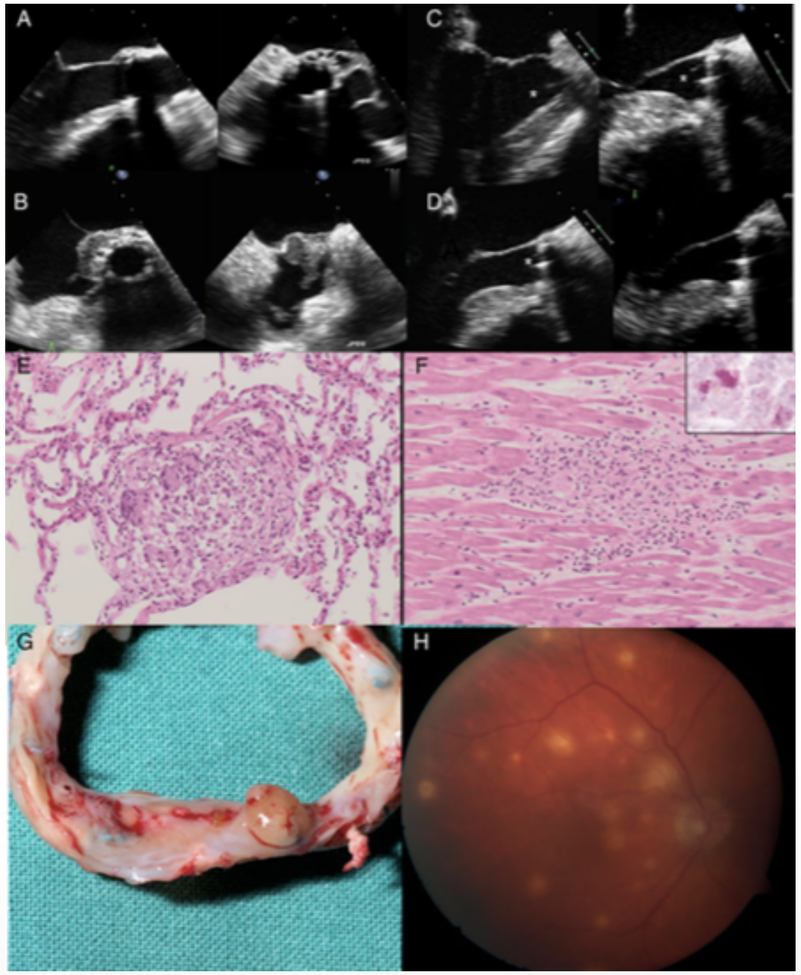

10 patients (Switzerland, Germany, Netherlands)

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

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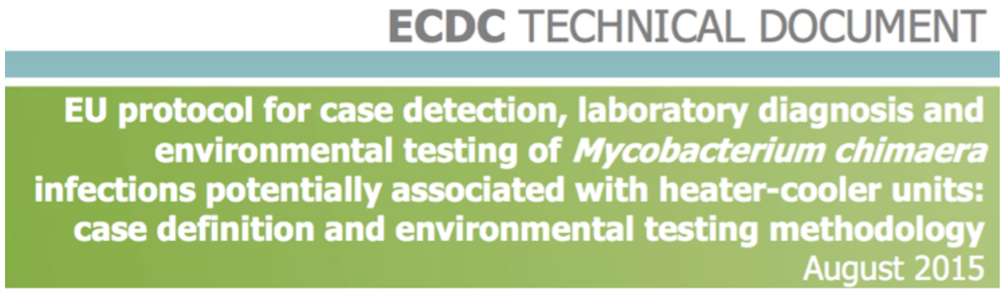

European Centre for Disease Prevention and Control. EU protocol for case detection, laboratory diagnosis and environmental testing of *Mycobacterium chimaera* infections potentially associated with heater-cooler units: case definition and environmental testing methodology. Stockholm: ECDC; 2015

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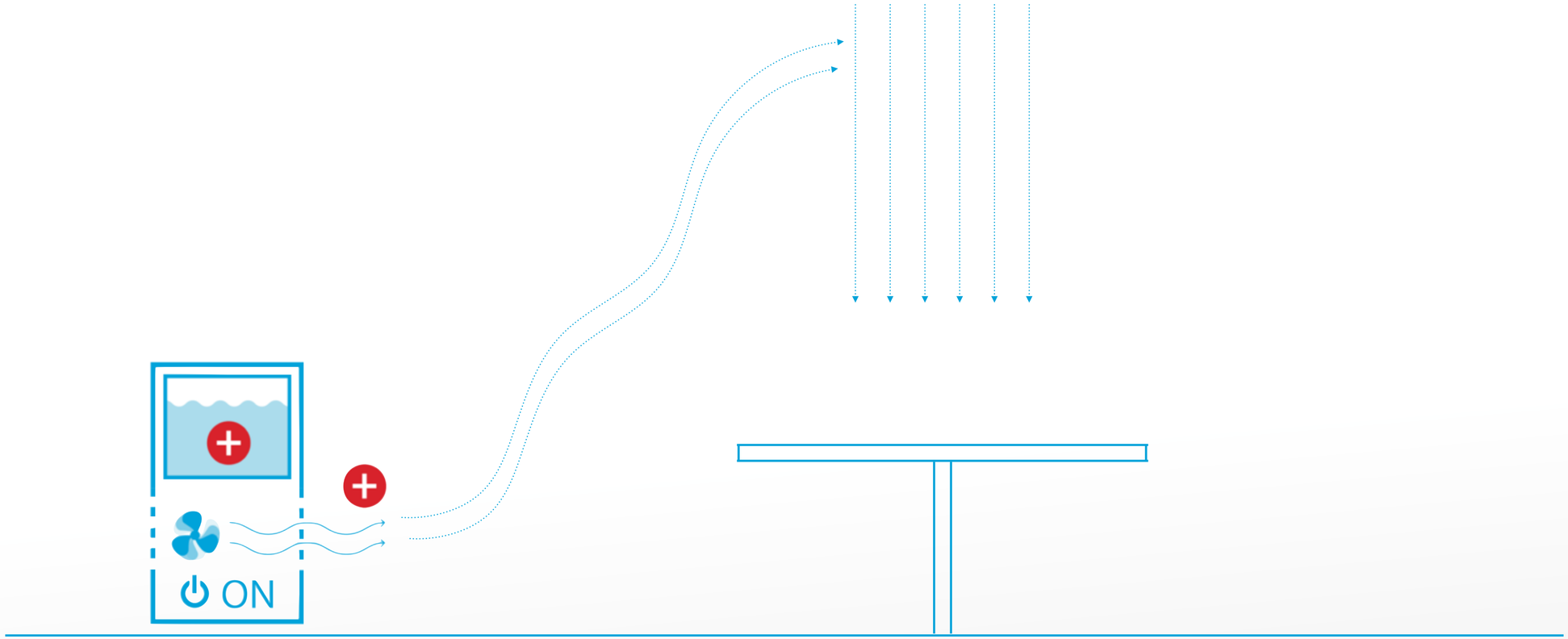

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Experience with cases

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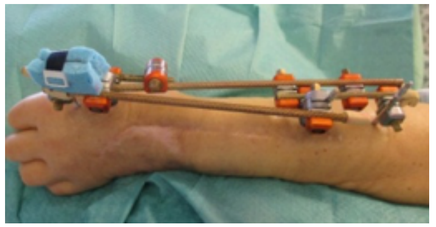
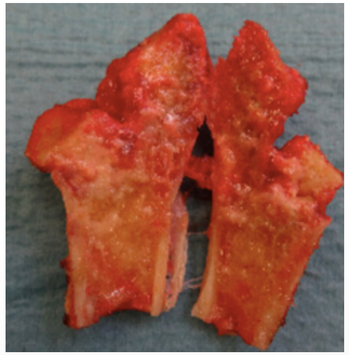

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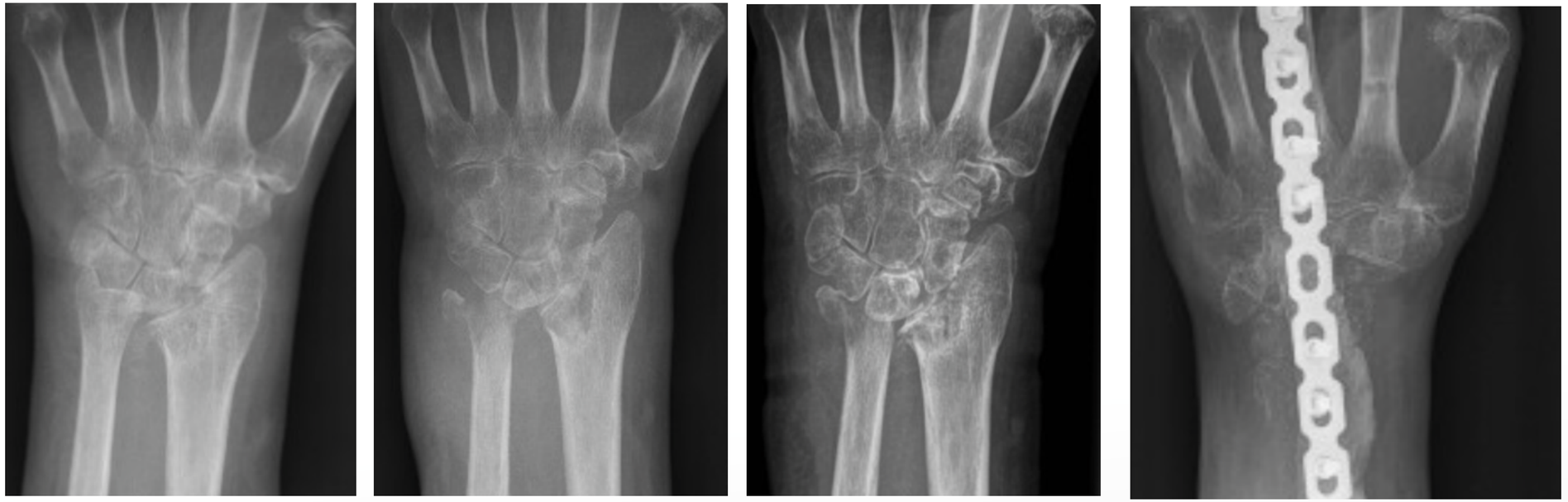

Biopsy cultures test negative after 9 months under AB Rx and multiple debridements

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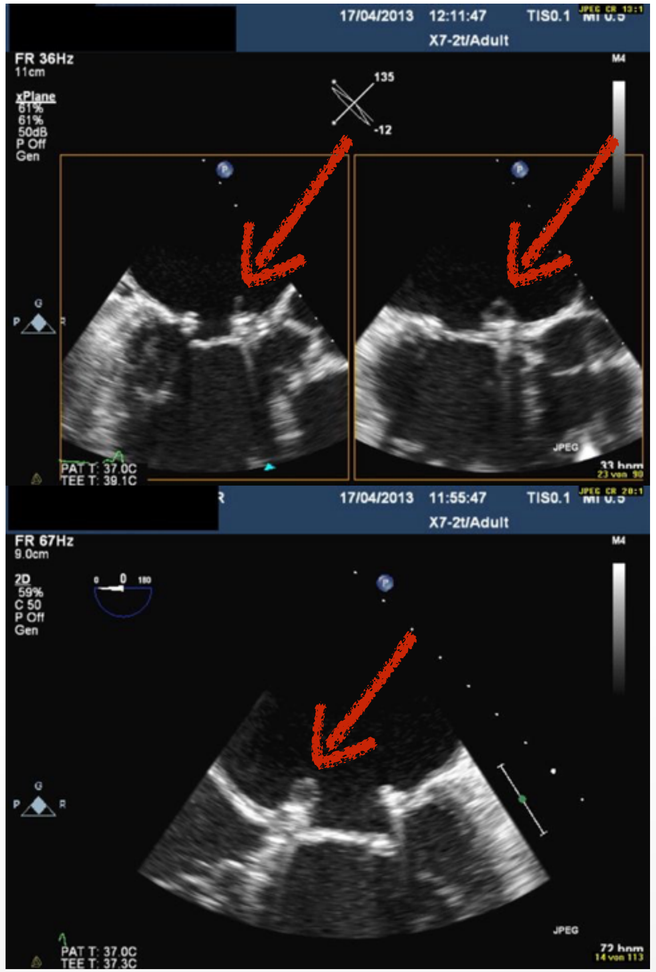
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61%
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-12
PAT T: 37.0C
TEE T: 39.1C
17/04/2013 11:55:47 TIS0.1
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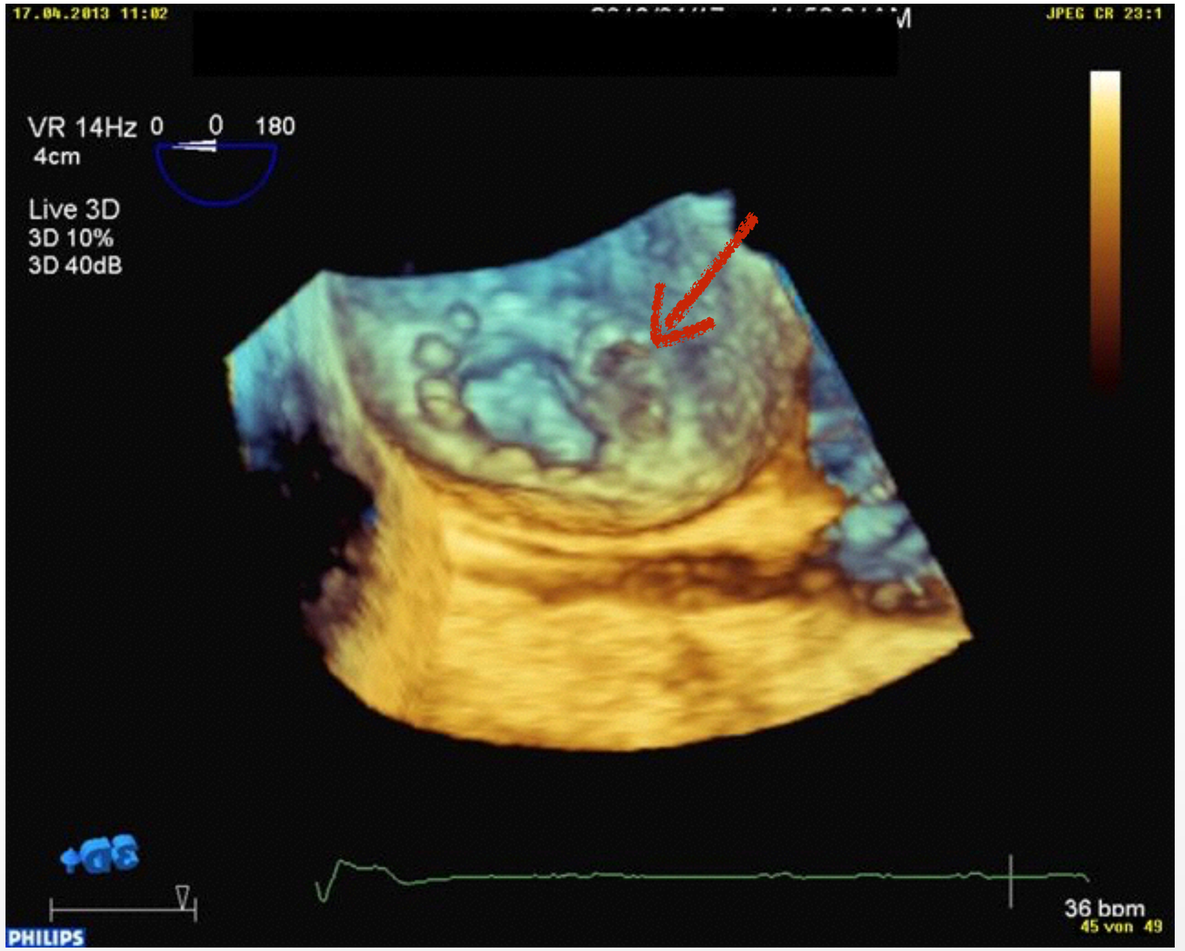
Gen
PAT T: 37.0C
TEE T: 37.3C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VR 14Hz 0 0 180
4cm
Live 3D
3D 10%
3D 40dB
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36 bpm
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M. chimaera still grows after 1 year of AB Rx

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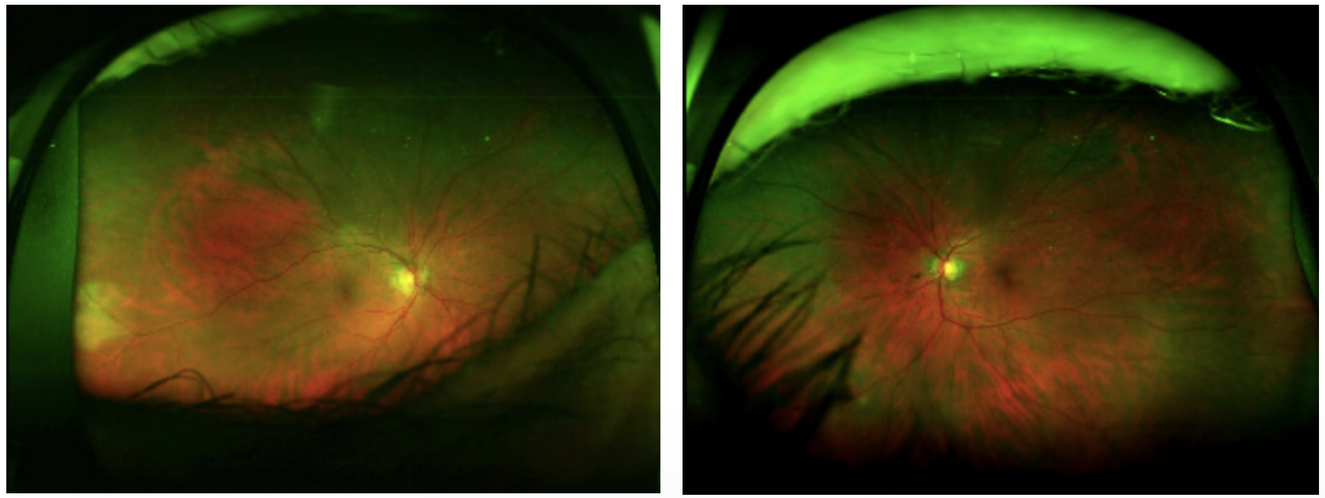

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Prevention?

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Intensified (Zurich) protocol

Daily water changes from 2014

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Separating heater-cooler unit from operating room air

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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

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Specific questions by FDA

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: M**ycobacteria 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**

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Take-home message:

Look for it!

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