

Global *Mycobacterium chimaera* Outbreak in Cardiac Surgery
Hugo Sax and Barbara Hasse, University of Zurich Hospital
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Global *Mycobacterium chimaera* outbreak in cardiac surgery

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University Hospital of Zurich
University of Zurich
Zurich, Switzerland



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World Health Organization, Geneva



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March 16, 2016

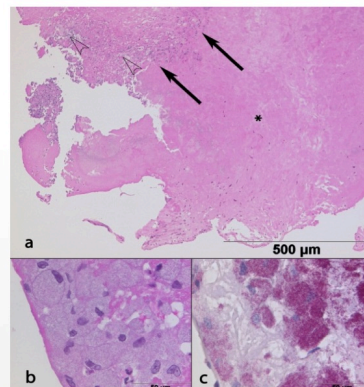
Prosthetic valve endocarditis mitral valve

Case #1 | 58-year-old male

2008 Mitral annuloplasty ring

2010 Dx of systemic sarcoidosis

2011 Respiratory distress, severe mitral and aortic valve insufficiency, at surgery fraying of ring and valve destruction...



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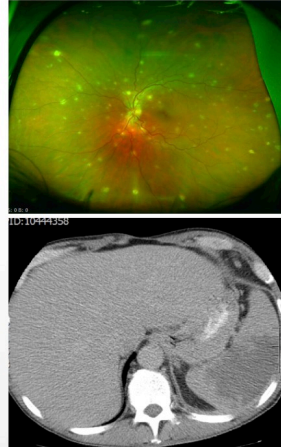
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Fever of unknown origin and composite graft infection

Case #2 | 58-year-old male

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

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



2012 Exodius due to splenic rupture

Mycobacterium chimaera: what is known

Microbiology

Slow growing non-tuberculous mycobacterium

Acid-fast, non-motile and non-spore forming coccobacilli

Formerly classified as *Mycobacterium intracellulare*, described by Tortoli 2004

Clinics

Lung disease among immunocompromised/elderly patients

Assumed as «less virulent....»

Environment

Not found in water systems in Europe, but the US

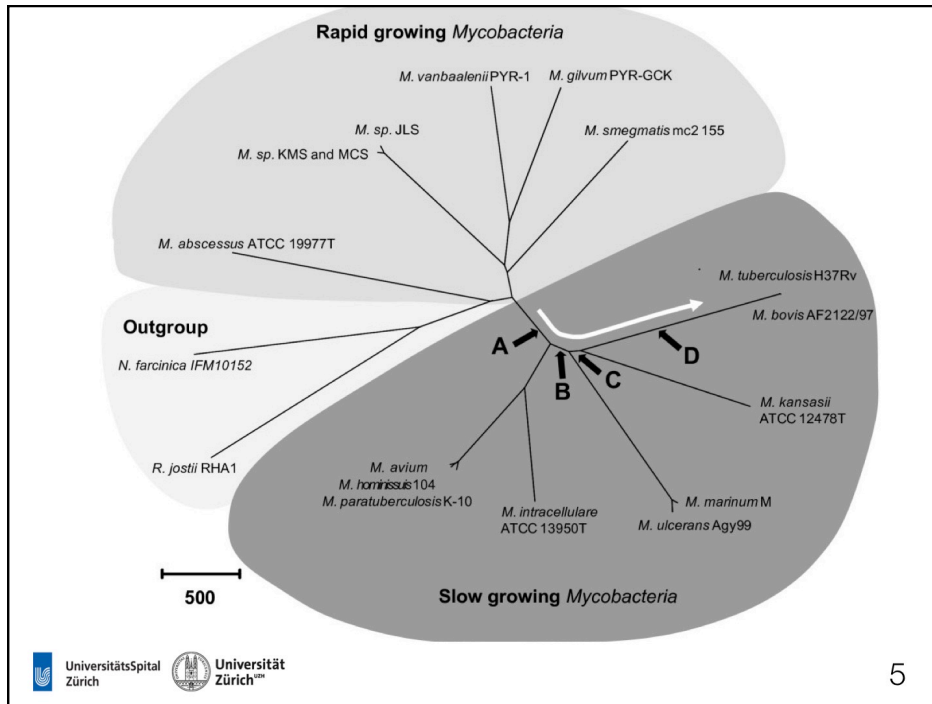


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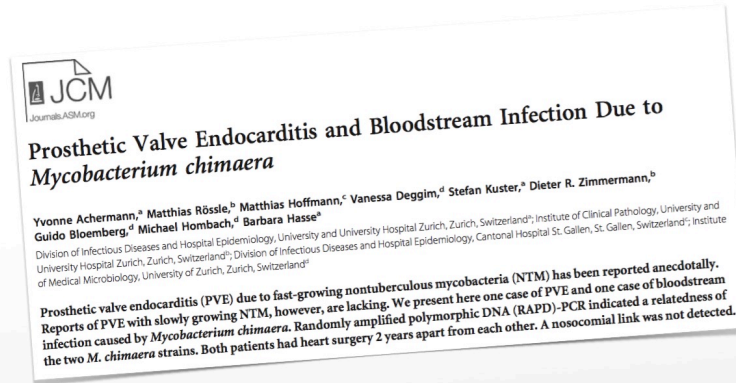
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Really «less virulent»...?!



Operated two years apart at the same hospital with a rare pathogen



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Achermann Y, et al. J Clin Microbiol. 2013 Jun;51(6):1769-73.

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Cluster

Two or more cases of a relatively uncommon event or disease related in time and/or place **perceived** to be greater than expected by chance.

Outbreak

The occurrence in a community or region of cases of an illness with a frequency **clearly** in excess of normal expectancy.

The number of cases indicating presence of an outbreak will vary according to the infectious agent, size and type of population exposed, previous experience or lack of exposure to the disease and time and place of occurrence.



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Randomly amplified polymorphic DNA (primers according *M. abscesses*)

No other matching strains found in hospital

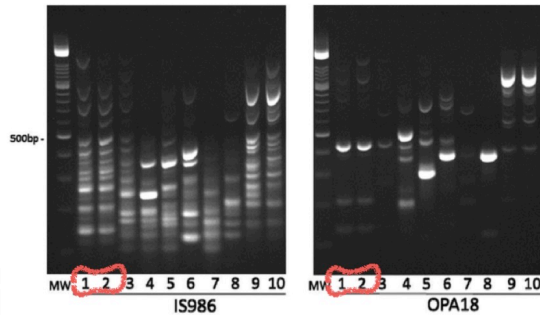


FIG 2 *Mycobacterium chimaera* strain typing using randomly amplified polymorphic DNA (RAPD)-PCR. Shown are RAPD-PCR patterns of *M. chimaera* clinical isolates from the two patients (lane 1, patient 1; lane 2, patient 2) and of eight respiratory culture isolates from eight different patients (lanes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

Outbreak investigation

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

Observations

Video analysis

Interviews

Workflow analysis

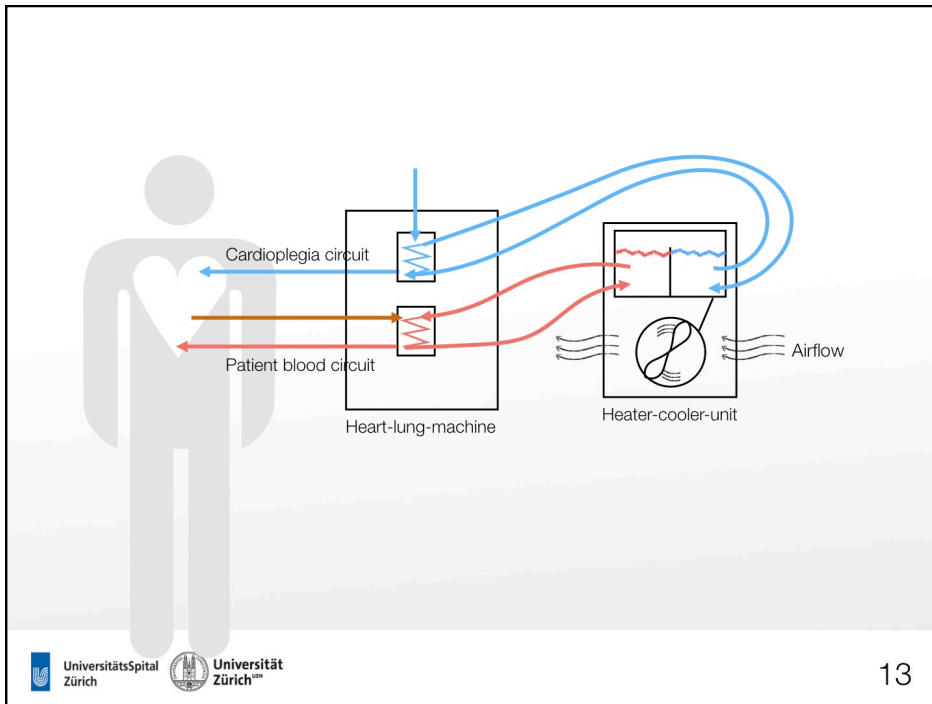
Mycobacteria cultures Patient heating blanket water circuit
Heater-cooler unit water tanks/circuits
Showers
Drinking water fountains

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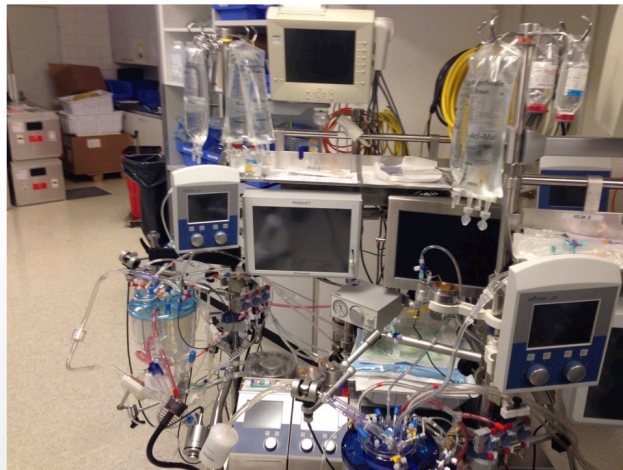
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Heart-Lung-machine



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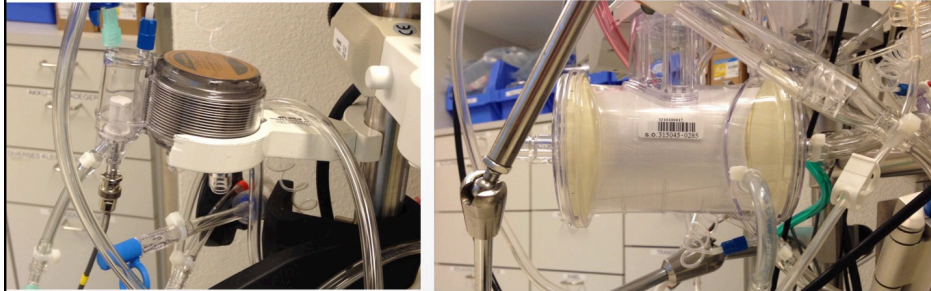
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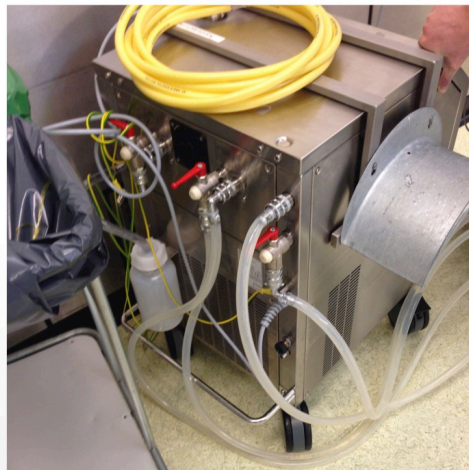
Heat-exchangers

Cardioplegia solution

Patient blood circuit

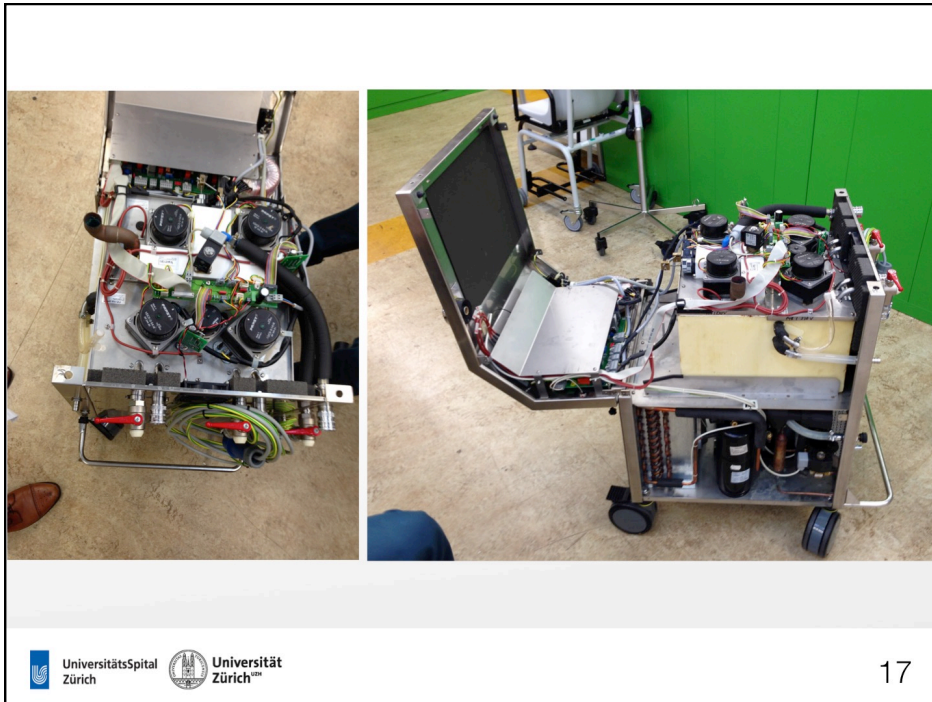


Sorin Stockert T3



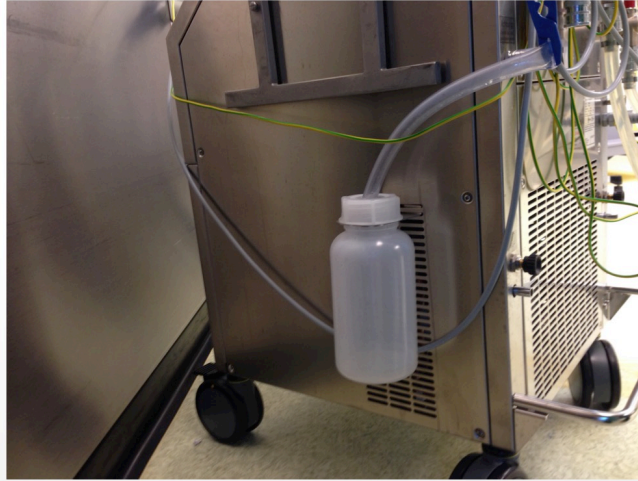
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Air cultures with heater-cooler unit turned on
Air cultures with heater-cooler unit turned off

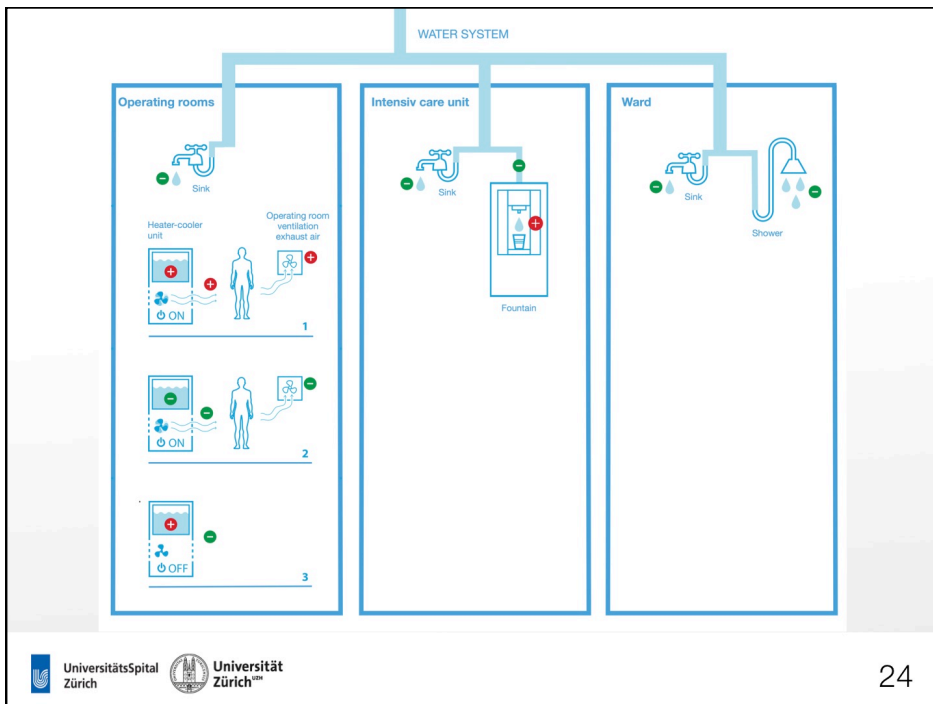
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Air cultures with heater-cooler unit turned on
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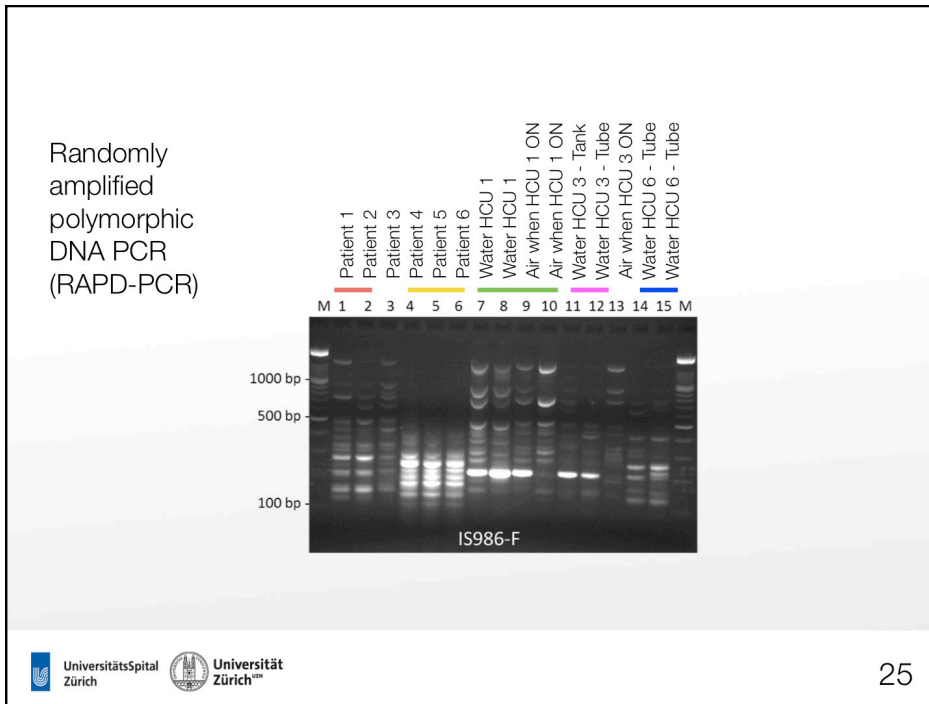


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Many outbreaks of surgical site infections with NTM

Report	Outbreak period	No. of cases	Region	Surgical procedures (no. of cases)	Clinical manifestation (no. of cases)	Etiology	Typing method	Clustering	Source	Source or mode of transmission
Robicsek F, et al. [1]	1976	19	North Carolina, USA	Aorto-coronary bypass (14), valve prosthesis (3), porcine valves (2), ventricular septum repair (1)	Sternal wound infection; latency 6-40 days (median, 14); 5 fatal cases	<i>M. chelonae</i> subspecies abscessus	--	--	Not identified	Unresolved
Hoffman PC, et al. [3]	1976	5	Colorado, USA	Coronary artery bypass (3), coronary grafts, and aortic valve (1), mitral commissurotomy (1)	Sternal wound infection; latency 6-44 days (median, 25 days); no fatal case	<i>M. fortuitum</i>	--	--	Not identified	Unresolved
Szabo L, et al. [2]	1977	6	Hungary	Open-heart surgery* not further detailed	Sternal wound infection; 3 fatal cases	<i>M. chelonae</i> , <i>M. abscessus</i>	--	--	Not identified	Unresolved
Kuritsky JN, et al. [4]	1981	6	Texas, USA		Sternal wound infection (4), endocarditis (1), saccharous graft-site infection (1); latency 21-52 days (median, 56); 2 fatal cases	<i>M. fortuitum</i> biovar fortuitum (4), <i>M. chelonae</i> subspecies abscessus (2)	--	--	Municipal water, tap water in operating room, water from ice machines; positive for <i>M. fortuitum</i> ; ice water for cooling of cardioplegia solution; many water sources positive for NTM; cardiologic swabs of scissors positive for <i>M. chelonae</i>	Hypothesis: hand transmission from cooling solution to surgical field
Yew WW, et al. [5]	1987-1989	21	Hong Kong, SAR	Aortic valve replacement (4), coronary artery bypass (9), mitral valve replacement (6), others	Sternal wound infections; fatality not reported	<i>M. fortuitum</i> bio var fortuitum (4), <i>M. fortuitum</i> complex	Plasmid profiles, rRNA restriction analysis	2 clusters of 9 and 6 cases	Not identified	Unresolved
Vukovic et al. [7]	2009	3	Serbia	Septum defect patching	Endocarditis	<i>M. fortuitum</i>	Enterobacterial repetitive intergenic consensus PCR	1 cluster of 3 cases	Contaminated patch stored in 2% propylene oxide between interventions	Patch
Strabell et al. [6]	1999-2008	13	Brazil	Mitral or aortic valve replacements	Endocarditis	<i>M. chelonae</i>			Contaminated prosthetic material by manufacturer	Valve
Nigpal et al. [8]	2008-2001	6	Minnesota, USA	Aortic valve replacement (4), aortic arch repair (1), tricuspid valve replacement (1), lung transplant (2)		<i>M. wolinskyi</i>	PCR restriction fragment analysis	1 cluster of 3, another case 'locally related'	Cold air blaster, heater-cooler-unit incriminated but no growth of <i>M. wolinskyi</i> from these sources	Unresolved
Current report	2008-2012	x	Switzerland		Endocarditis, sternal, vertebral, ulnar osteitis, disseminated disease	<i>M. chimaera</i>	RAPD-PCR	2 clusters of 2 and 3 patients	Heater-cooler-unit water tank of heart-lung-machine	Airborne

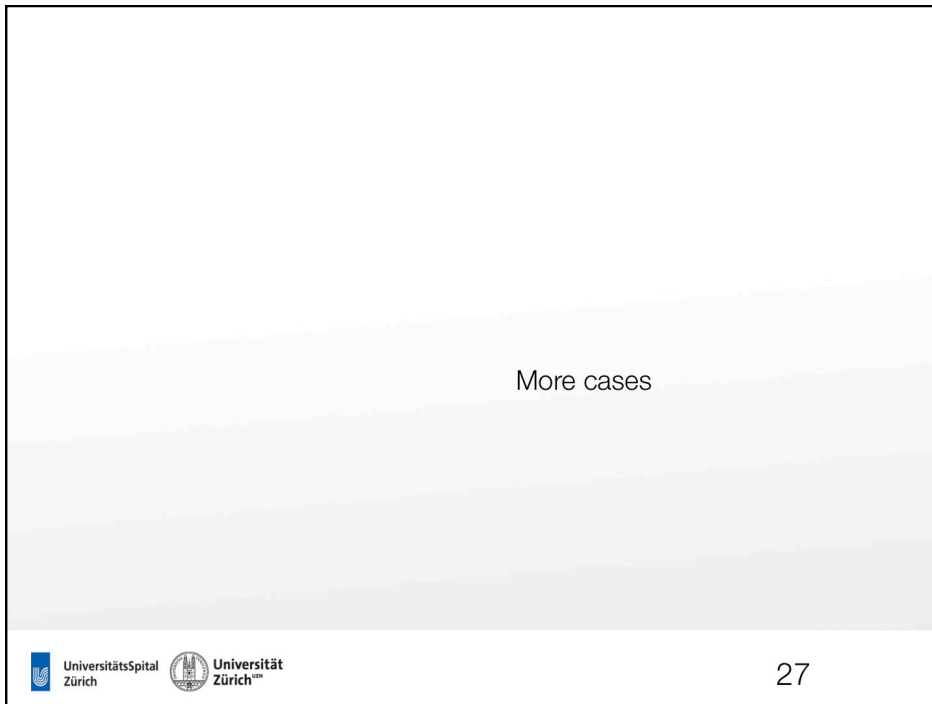
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Mitral ring endocarditis

Case #3 | 61-year-old male
2009 Mitral valve reconstruction
2012 Arthritis due to *M. chimaera*
2013 Mitral ring endocarditis
2014 Redo surgery

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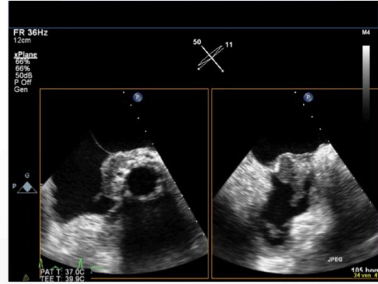
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Aortic prosthetic valve endocarditis

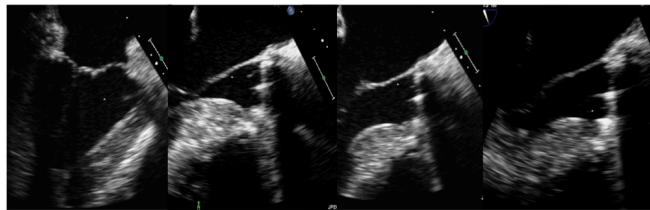
Case #4 | 49-year-old male with Crohn's disease

Treatment with azathioprin
2009 Aortic valve replacement
2013 Progressive Dyspnea,
Ascites, icterus



Prosthetic valve endocarditis
Redo surgery

Composite graft infection



Case #5 | 59-year-old male

2010 Composite graft replacement
2013 Spondylodiscitis
2014 Composite graft infection due to *M. chimaera*
2014 Redo surgery

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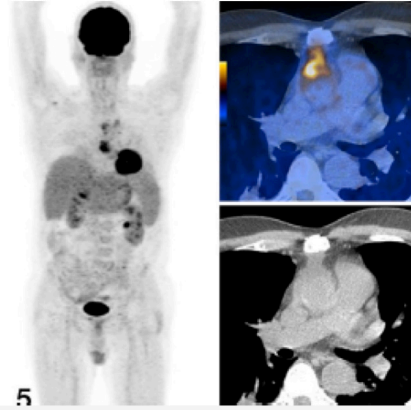
Aortic arch infection

Case #5 | 60-year-old male

2010 Aortic arch replacement

2014 Aortic graftinfection due to *M. chimaera*

2014 Debridement of periaortic tissue, retention of graft



Grade 5, focal and intense FDG-uptake plus fluid collections/abscess formation

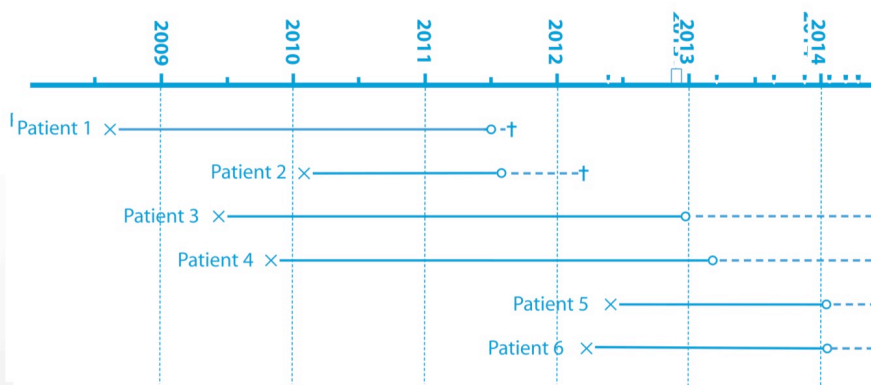


Sah BR. Eur J Vasc Endovasc Surg (2015) -, 1e103.



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Time line of infections



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Prostheses differed in materials and manufacturers

	Age (years)	Date of index surgery	Latency (years)	Heart surgery	Implant	Material	Manifestations	Positive cultures for <i>Mycobacterium chimaera</i>	Histopathology
Patient 1* †	58	13.08.2008	2.9	Mitral valve reconstruction	28 mm C-E physio mitral annuloplasty ring (model 4450; serial no. 1716293, lot no. 08E134)	Layers of Elgiloy Sewing ring with layers of silicone covered by polyester knit fabric	Endocarditis, splenomegaly, pancytopenia, hepatitis, renal involvement	Blood, cardiac tissue prosthesis, sputum	Granulomatous hepatitis, nephritis
Patient 2* †	51	29.01.2010	1.5	Composite graft for aortic dissection	25 mm ATS composite graft (serial no. 408656, lot no. 502AG23) 8 mm GAHE Gelweave x prosthesis (serial no. 0001079637, lot no. 1013851A 1577)	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	12.06.2009	3.6	Mitral valve reconstruction	32 mm x 2 mm Carpenlier ring (model 445, serial no. 1984171, lot no. 09B052)	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	31.10.2009	3.4	Aortic valve replacement	24 mm ATS Open Pival AP Series Heart Valve (model 505DA24, serial no. 408100)	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	30.05.2012	1.7	Aortic root and arch replacement	ATS AVG (model 502AG23, serial no. 523707) 26 mm graft as elephant trunk (model IGW0026-30/serial no. N 40552231, lot no. 11J15)	Valve: pyrolytic carbon; Hemiarch: 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	26.03.2012	1.8	Aortic root and arch replacement	Medtronic Freestyle Aortic Valve (model 755004035, serial no. 22026x09m, 50 cm Vasutek (serial no. 0001193041, lot no. 1049981967) 10 mm Gelweave D, 10 mm, L, 15 cm (serial no. 0001343672, lot no. 1195641 3441)	Biological Polyester	Vascular graft infection, splenomegaly, hepatitis, renal failure, multifocal chorioiditis	Cardiac tissue and prosthesis	Granulomatous interstitial nephritis

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 further patient at that time

Going public

July 14, 2014




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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 Kohler¹, Stefan P. Kuster¹, Guido Bloemberg², Bettina Schulthess^{2,3},
Michelle Frank⁴, Felix C. Tanner⁴, Matthias Rössle⁵, Christian Böni⁶, Volkmar Falk^{7,8},
Markus J. Wilhelm⁷, Rami Sommerstein¹, Yvonne Achermann¹, Jaap ten Oever⁹,
Sylvia B. Debast¹⁰, Maurice J.H.M. Wolhagen¹⁰, George J. Brandon Bravo Bruinsma¹¹,
Margreet C. Vos¹², Ad Bogers¹³, Annerose Serr¹⁴, Friedhelm Beyersdorf¹⁵, Hugo Sax¹,
Erik C. Böttger^{2,3}, Rainer Weber¹, Jakko van Ingen^{16†}, Dirk Wagner^{17†},
and Barbara Hasse^{1†*}**

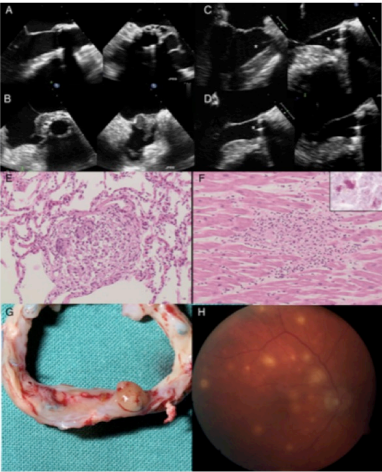


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10 patients (CH, D, NL)
 1-4 y latency since cardiac surgery
 Peripheral or systemic manifestations
 8/10 surgical re-intervention despite Rx
 6/10 break-through infections, 4 fatal
 3 patients are being monitored post-Rx



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Kohler et al. European Heart Journal 2015; doi: 10.1093/eurheartj/ehv342

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The screenshot shows two documents related to the *Mycobacterium chimaera* outbreak. On the left is an ECDC Technical Document titled "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 August 2015". On the right is a warning letter from the U.S. Food and Drug Administration (FDA) dated December 29, 2015, addressed to Sorin Group Deutschland GmbH, regarding the safety of heater-cooler units used in cardiac surgery. The FDA letter mentions that these units can harbor and disseminate *Mycobacterium chimaera*, which has caused outbreaks in cardiac surgery patients. The document also includes logos for the University of Zurich Hospital and the University of Zurich.

To our best knowledge

Switzerland	7 patients
Netherlands	4 patients
Germany	5 patients
UK	20 patients
Spain	1 patients
US	11 patients
France	2 patients
Irland	2 patients

And counting...

The slide also includes logos for the University of Zurich Hospital and the University of Zurich.

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Now the work starts for clinicians...

Invasive *M. chimaera* infections

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

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

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Culture negative PVE/ aortic graft infections
 High index of suspicion for *M. chimaera* infections needed

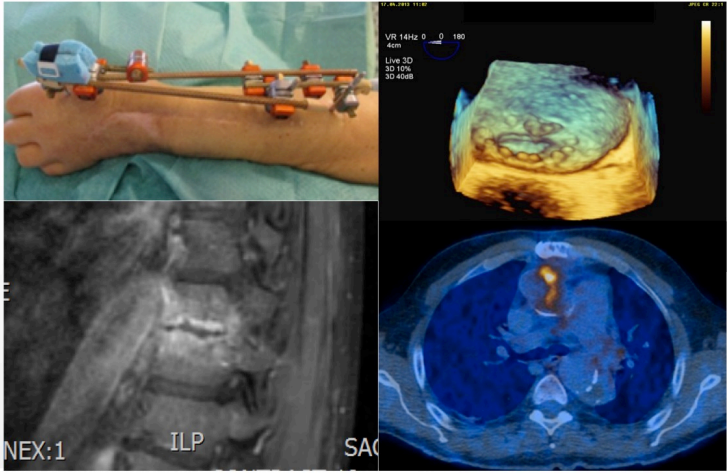
How to diagnose it: New differential for «culture-negative»


<p>Microbiology Positive heparin blood cultures for <i>M. chimaera</i> Detection of <i>M. chimaera</i> by culture or PCR in cardiac tissue in the proximity of the prosthetic material</p> <hr/> <p>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</p> <hr/> <p>Additional criteria Negative conventional blood cultures Serologic exclusion of <i>Coxiella</i>, <i>Bartonella</i>, <i>Brucella</i>, <i>Tropheryma whippeli</i>, <i>Legionella</i>, <i>Mycoplasma</i>, <i>Chlamydia</i></p>	<table border="1"> <tr><td>Brucella spp</td></tr> <tr><td>Coxiella burnetii</td></tr> <tr><td>Bartonella spp</td></tr> <tr><td>Tropheryma whippeli</td></tr> <tr><td>Mycoplasma spp</td></tr> <tr><td>Legionella spp</td></tr> <tr><td>Mycobacterium chimaera</td></tr> </table>	Brucella spp	Coxiella burnetii	Bartonella spp	Tropheryma whippeli	Mycoplasma spp	Legionella spp	Mycobacterium chimaera
Brucella spp								
Coxiella burnetii								
Bartonella spp								
Tropheryma whippeli								
Mycoplasma spp								
Legionella spp								
Mycobacterium chimaera								


 Kohler et al. European Heart Journal 2015; doi: 10.1093/eurheartj/ehv342
 Abela I, Günthart H. Herzgefäss 6/2015

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Presentation often atypical and delayed
 Extracardiac manifestations of precede cardiac manifestations

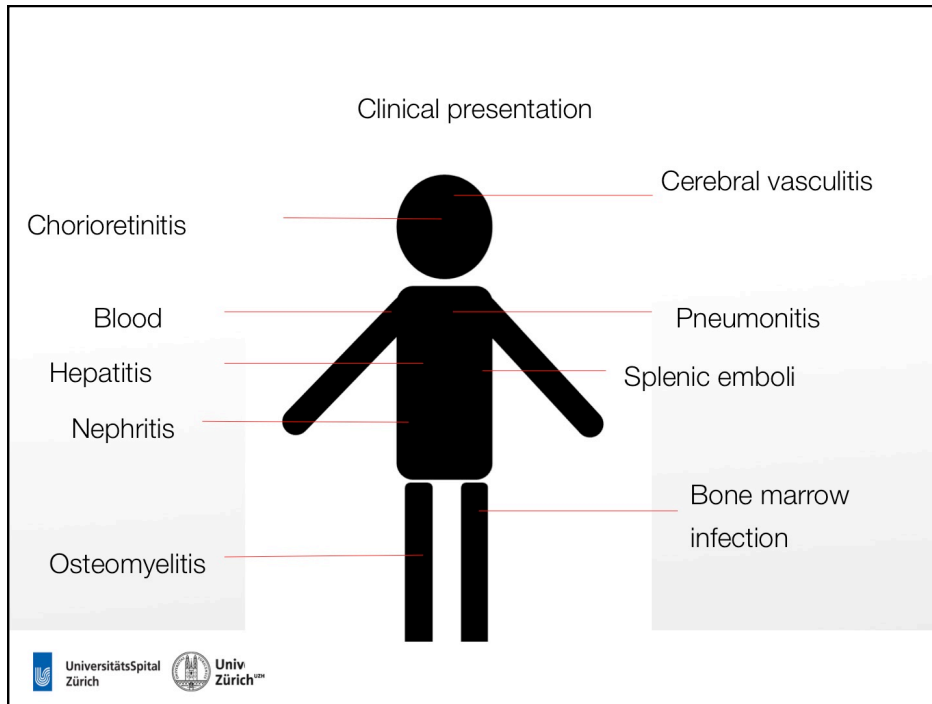



 Kohler et al. European Heart Journal 2015; doi: 10.1093/eurheartj/ehv342

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Anterior and posterior uveitis/ chorioretinitis

51 year old male
 Multifocal choroidal lesions

Multiple flat, cream colored lesions with indistinct border

Depending on the activity status of the lesion they appeared hyper- or hypoautofluorescent

Zweifel S et al., Div of Ophthalmology USZ 46

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Treatment

Multidisciplinary approach!



- Infectious disease specialist
- Microbiologist
- Cardiovascular surgeon
- Cardiologist
- Cardiac anesthesia
- Nuclear imaging specialists
- Ophthalmologist

Ocular manifestations are good indicators of the systemic control of the disease process



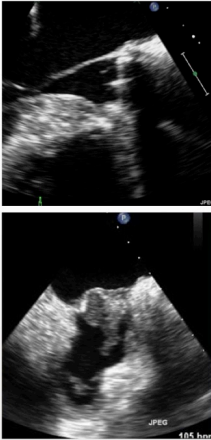



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Treatment		
<p>Lead-in phase:</p> <p>Clarithromycin Rifabutin Ethambutol +/- Amikacin Moxifloxacin</p> <p align="center">Goal:</p> <p>Reduction of bacterial load</p>	<p>Redo-Operation:</p> <div style="text-align: center;">  <p>«Sine qua non»</p> </div> <p align="center">Goal:</p> <p>Removal of biofilm-forming strains</p>	<p>Chronic phase:</p> <p>Clarithromycin Rifabutin Ethambutol +/- Amikacin Moxifloxacin</p> <p align="center">Goal:</p> <p>Treatment, hindrance of new dissemination</p>
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Break-through infections occur without removal of cardiac devices

 <p>Embolic events</p>	 <p>Epicardial left wire infection</p>	 <p>Endocarditis</p>
		50

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Drug susceptibility of *M. chimaera* isolates

Table 2 Phenotypic drug susceptibility testing of 15 *M. chimaera* isolates of the 10 study patients

Patients	1	2	3	4	5	6	7	8	9	10					
Sample date	30.06.11	27.07.11	10.05.12	20.03.13	07.02.14	06.03.13	13.06.13	06.01.14	10.09.14	14.01.14	26.11.14	12.06.13	23.04.13	16.01.13	30.01.13
Material	Mitral ring	Bone marrow	Urine	Bone Wrist	Mitral ring	Cardiac tissue	Pocket tissue	Vertebral bone	Urine	Cardiac tissue	Blood culture	Aortic valve	Mitral valve	Bone	Cardiac tissue
MIC (mg/L)															
Clarithromycin	≤4	≤4	≤4	≤4	≤4	≤4	≤4	≤4	≤4	≤4	≤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	4	4	4	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
Rifampicin	>1<20	>1<20	>1<20	4	4	ND	4	4	4	4	4	2	2	2	1
Rifabutin	>0.1<2	>0.1<2	>0.1<2	0.4	0.4	2	0.4	0.4	0.4	2	2	0.5	0.5	≤0.25	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.
 MGIT method applied in Patients 1–6, the broth dilution method has been applied in Patients 7–10.

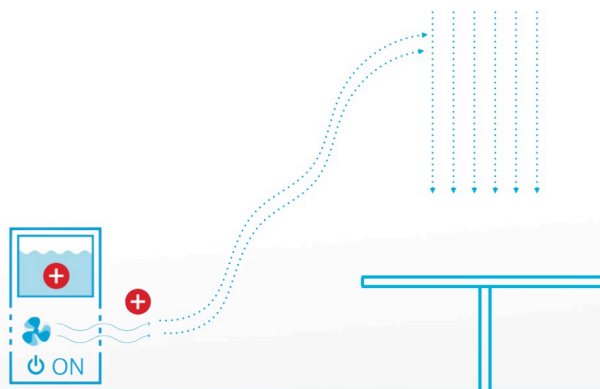
Situation in vivo/ on prosthesis?

Prevention

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Separating heater-cooler unit from operating room air



Sommerstein R, et al. Transmission of *Mycobacterium chimaera* from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System. *Emerg Infect Dis* 2016

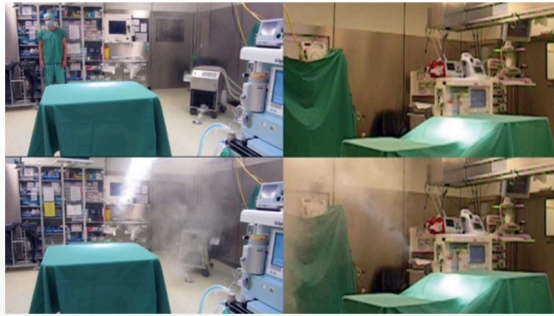
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Video of smoke experiments showing contamination of ultra-clean ventilation in OR

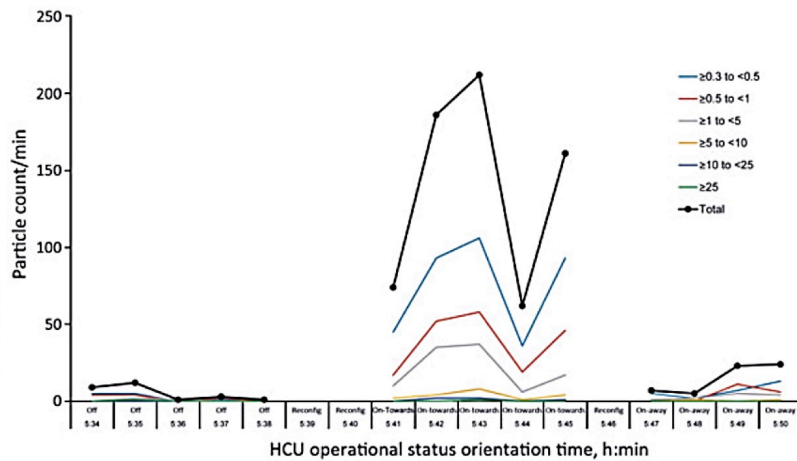


<https://youtu.be/YZ41aLoHrhQ>



Sommerstein R, et al. Transmission of *Mycobacterium chimaera* from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System. Emerg Infect Dis 2016

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Sommerstein R, et al. Transmission of *Mycobacterium chimaera* from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System. Emerg Infect Dis 2016

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Early diagnosis
Screening

Screening tools

Look for it !

Physical examination

Medical history

Heparin blood cultures, Perform mycobacterial cultures or

Mycobacterial specific PCR in case of biopsy

Histopathological work up (presence of granulomas)

Scrutinize Sarcoidosis, vasculitis or unknown systemic diseases

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Look carefully at fever of unknown origin or vasculitis with former cardiopulmonary bypass surgery

63 year-old lady

2008 History of aortic valve replacement

Fatigue, fevers, and weight loss.

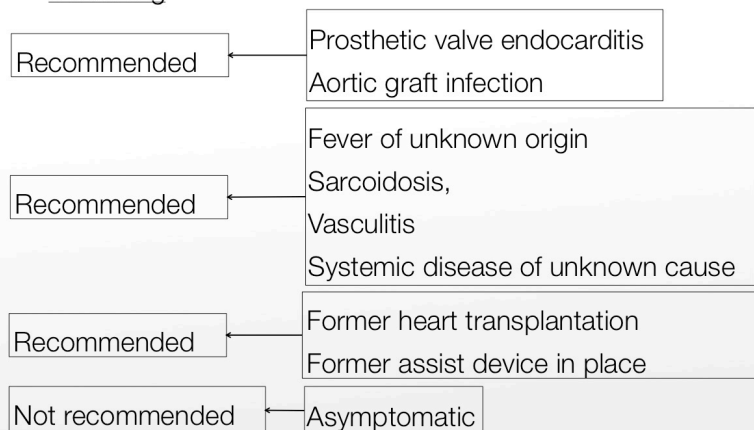
2011 Unknown vasculitis with 4/10 blood cultures positive for MAC

Retrospective review of echocardiography:

Endocarditis with strains

Screening approach among patients with former cardiopulmonary bypass surgery

Screening



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Missed diagnosis....

Look back for MAC/ *M. avium* cases
Look back for culture-negative PVE, aortic graft infection

Look back yielded around 20 cases of presumptive
cardiac infections with MAC with fatal outcome



Look back at University Hospital Zurich yielded no cases
Look back Switzerland: ongoing



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The story is still ongoing...

Conclusions

When a system can fail, it will fail (Murphy)

A note on common sense

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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Take-home message:

Look for it!

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The next WHO teleclass

April 20, 2016

**THE CORE COMPONENTS FOR INFECTION PREVENTION
AND CONTROL PROGRAMS AND ACTION PLAN**



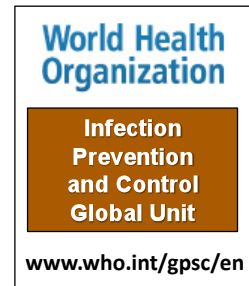
Jules Storr

Objectives:

- Outline the background and rationale
- Summarise the two-pronged approach
- Explore how the core components will contribute to the global knowledge
- Describe next steps and highlight how this work will strengthen approaches to IPC improvement and implementation across all countries

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