

Clinical management of *Mycobacterium chimaera* infection

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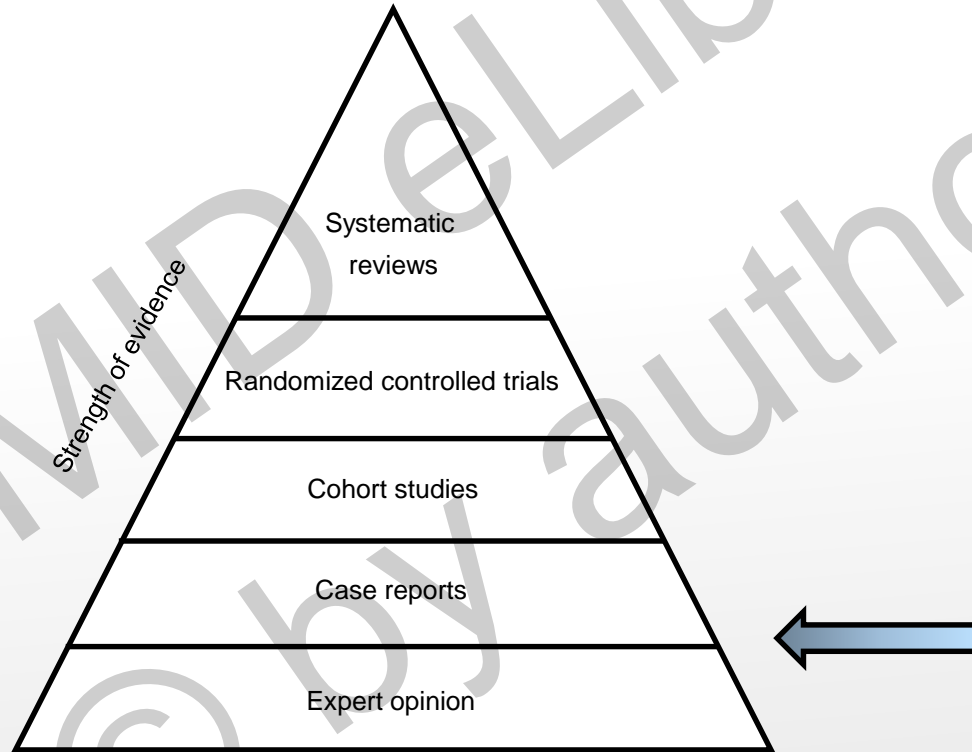
International Collaboration

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CDC: Heather Moulton, Lyman Meghan
ECDC: Diamantis Plachouras

Treating physicians/ patients/ relatives



Disclosure: Evidence level low



Action points for clinicians/ hospitals



Scope of the problem

Risk assessment

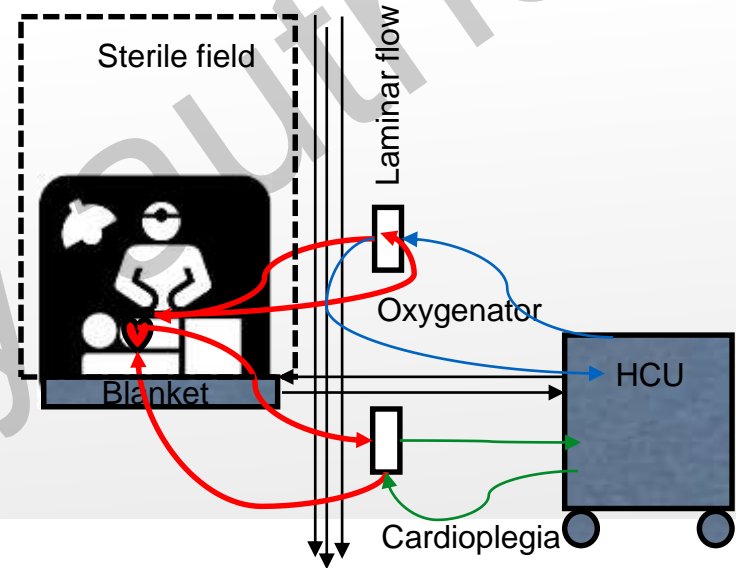
Screening

Diagnosis and clinical presentation

Clinical management

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- If withdrawn capacity of life-saving cardiac surgery affected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



Surveillance

- Screening
- Antibiograms
- Outcomes

Audit/ Feedback

- Multidisciplinary approach
- Consultant involvement
- Translational research
- Biofilm, NGS etc



Processes

- Infection prevention
- Diagnostics
- TDM
- Management side effects

Treatment approach/ Antibiotic choice

- Clinical algorithms
- Escalation/ De-escalation of treatment
- Surgical strategy

82 year old men: a disseminated case?

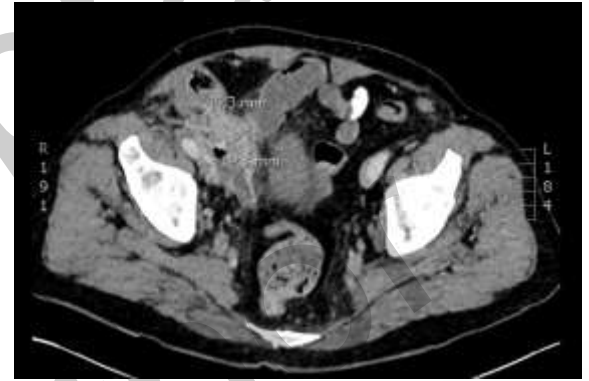
COPD, Coronary artery bypass surgery 2013

Presentation: Fever, weight loss, fatigue

Diagnosis: Perityphlitic abscess

Treatment: piperacillin/ tazobactam

Sputum: *Mycobacterium chimaera*



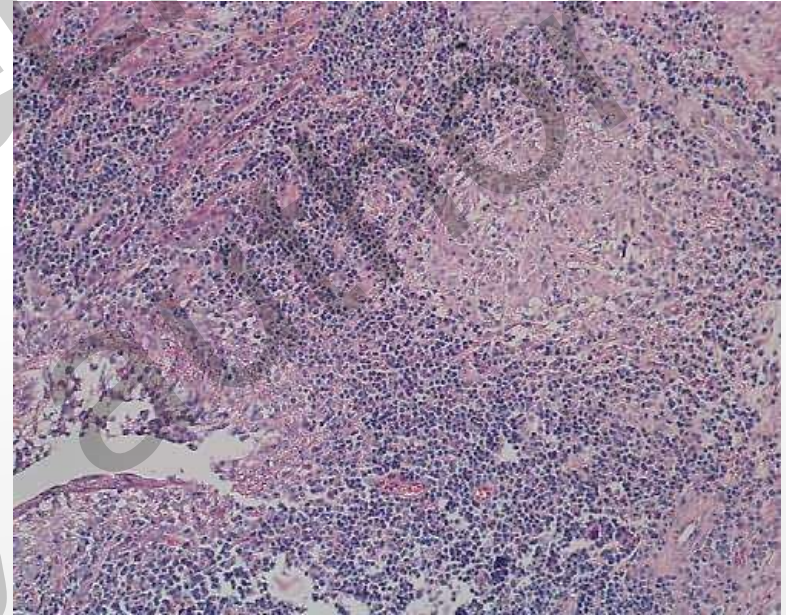
66 year old man with sarcoidosis: your diagnostic steps?

History of composite graft operation

Fatigue and weight loss

Pancytopenia, renal function deteriorating

Bone marrow and kidney with non-caseating granulomas



61 year old men: treatment?

History of mitral annuloplasty ring 2009
Therapy refractory course of an arthritis
of the left wrist under therapy with methotrexate
CRP 7.8 mg/L, Lc 4.39 G/L

Bone biopsy: microscopically acid fast bacilli
Culture: *Mycobacterium chimaera*



Action points for clinicians/ hospitals



Scope of the problem

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The risk of getting the infection is low

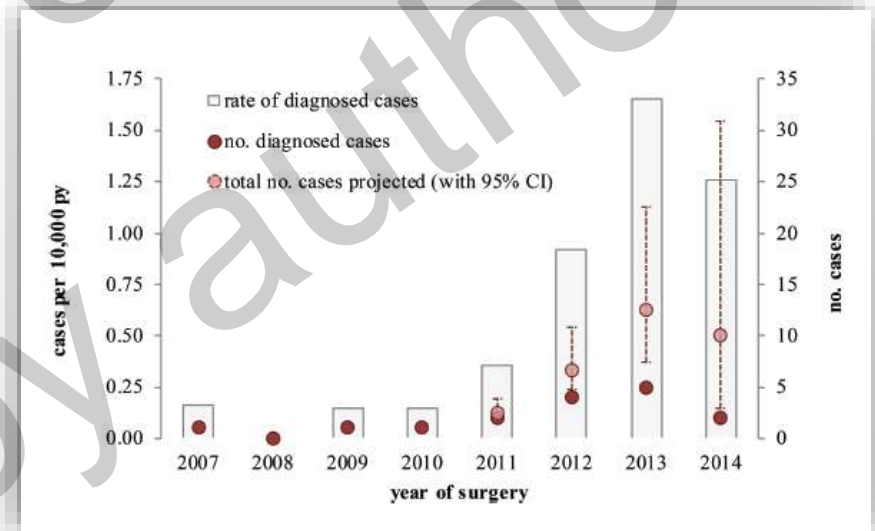
Our hospital

1:500 cases

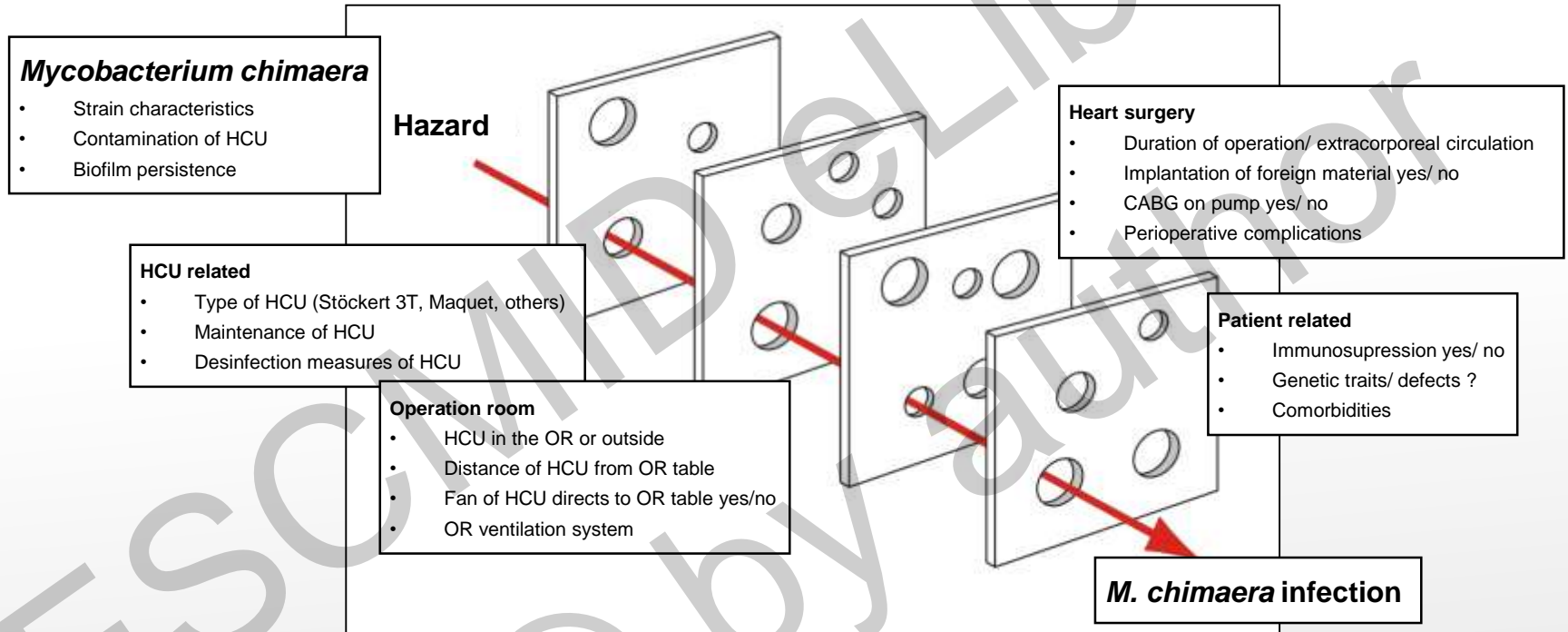


UK

0.39 cases per 10,000 PY



The stochastic phenomenon of getting the infection



Association with cardiovascular implants

Case number	Age (years)	Sex	Cardiac surgery centre	Type of surgery (exposure)	Prosthetic material	Site of infection	Death due to infection	Incubation period (years) ^a
1	80	Male	A	Aortic valve replacement	Yes	Endocarditis	No	<1
2	75	Male	B	CABG	No	Spondylodiscitis	No	5
3	65	Male	C	Aortic valve replacement	Yes	Valvular aortic endocarditis, paravalvular leak and abscess	Yes	3
4	67	Male	C	CABG and aortic valve replacement	Yes	Paravalvular abscess ^c	No ^b	4
5	53	Male	C	Aortic valve replacement	Yes	Endocarditis and cerebral abscesses	No	3

Valve replacement or repair

Aortic vascular grafts, left ventricular assist devices, heart transplant

Sternal wound infections after on pump coronary artery bypass surgery

Lung transplantation (?)

82 year old men: **No** disseminated case

COPD, Coronary artery bypass surgery 2013

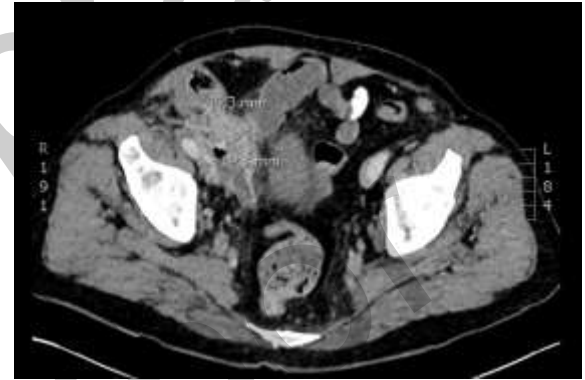
Presentation: Fever, weight loss, fatigue

Diagnosis: Perityphilitic abscess

Treatment: piperacillin/ tazobactam

Sputum: *Mycobacterium chimaera*

ON/ OFF pump CABG



Action points for clinicians/ hospitals



Scope of the problem

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Systematic screening versus screening of persons considered «at risk»

Pros

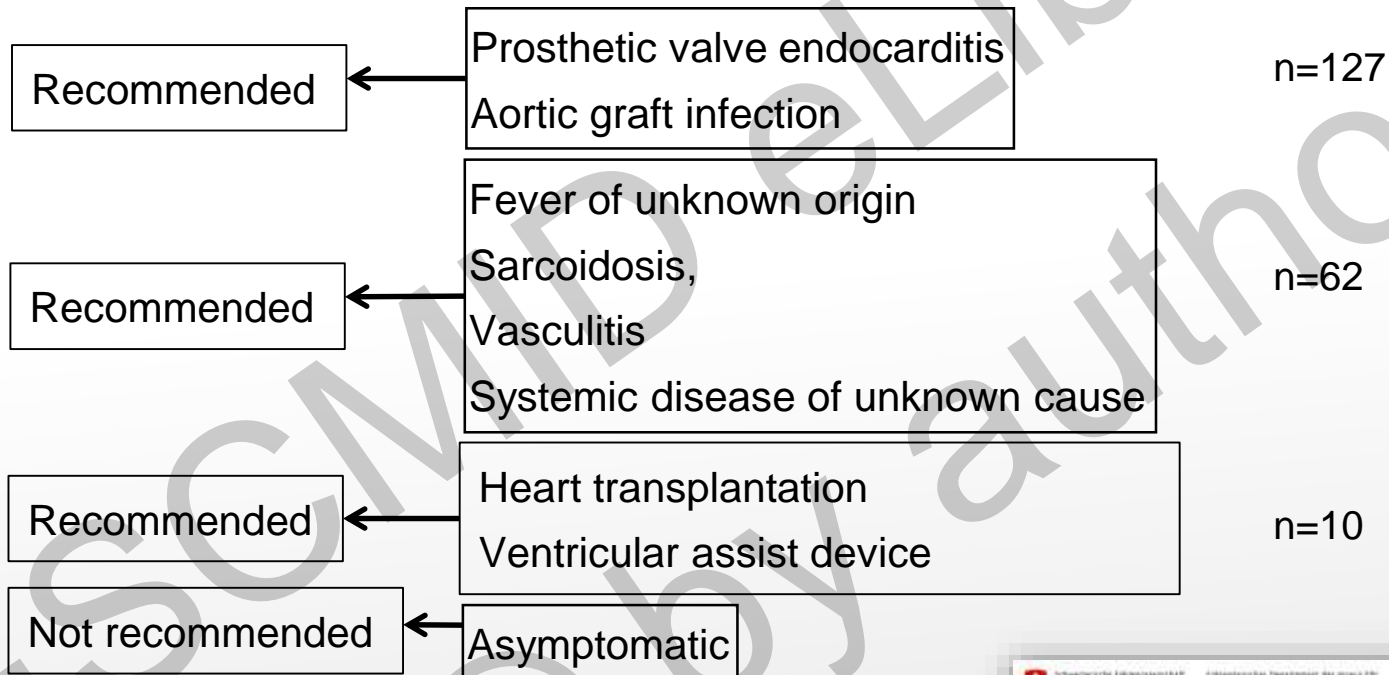
- Enables patients to be vigilant
- Earlier diagnosis
- Possible prevention of systemic spread of infection



Cons

- Latency 21 month
- Methods to diagnose *M. chimaera* infection have low negative predictive value
- Patients with negative investigation must be re-assessed repeatedly for years
- Psychological impact for patients, costs

Screening of persons considered «at risk»



Mycobacterium chimaera: The ethical duty to disclose the minimal risk of infection to exposed patients

The screenshot shows a legal website with a navigation bar at the top containing links like 'HOME', 'HOT LEGAL STORIES', 'LEGAL NEWS', 'POTENTIAL LAWSUITS', 'LAWYSTER FEELS', 'SETTLEMENTS', 'STATE LAW', 'VIDEO', and 'RSS'. A search bar is present. Below the navigation is a banner for 'LegalShield' with the text 'Affordable Access to Legal Advice When You Need It'. The main content area features the article title 'Stockert 3T Heater-Cooler System Infection and Stockert Lawsuits'. The article text discusses the 'Stockert 3T heater-cooler system' and its link to infection during certain surgeries, mentioning the CDC and FDA. It also mentions 'M. chimaera' and 'transient bacteria via water into patients, especially during open-heart cardiac surgeries'. There are several sub-sections with images and text, including 'STOCKERT 3T LEGAL ARTICLES AND INTERVIEWS', 'STOCKERT 3T Heater-Cooler System: Letter: Evidence, Explanation of Apology?', 'STOCKERT 3T Heater-Cooler System: Confusion and Concerns', and 'Surgery Patients Deserve Heading for Potentially Deadly Infection as Class Action'. A 'FREE CASE EVALUATION' box is also visible. At the bottom left, there is a diagram of the Stockert 3T heater-cooler system.

Information of 17,000 patients

- 2 patients referred for testing

Possibility of litigation

- Disclosure of the risk of *M. chimaera* infection to patients ?

Nguyen A et al. J Thorac Cardiovasc surg: 2017; 1-3
The Washington Post (Oct. 13, 2016)

Action points for clinicians/ hospitals



Scope of the problem

Risk assessment

Screening

Diagnosis and clinical presentation

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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

Extracardiac manifestations may precede cardiac



Chorioretinitis

Cerebral vasculitis

Pancytopenia

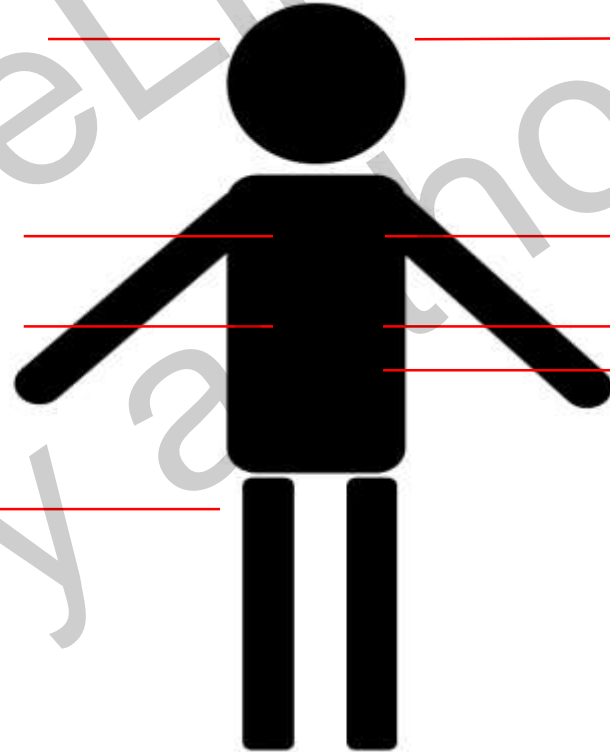
Pneumonitis

Hepatitis

Splenomegaly

Nephritis

Osteomyelitis



61 year old men: **TEE** needed

History of mitral annuloplasty ring 2009
Therapy refractory course of an arthritis
of the left wrist under therapy with methotrexate
CRP 7.8 mg/L, Lc 4.39 G/L

Bone biopsy: microscopical acid fast bacilli
Culture: *Mycobacterium chimaera*



Dangers for misdiagnosis

New differential for „culture negative“

Brucella spp
Coxiella burnetii
Bartonella spp
Tropheryma whippelii
Mycoplasma spp
Legionella spp
Mycobacterium chimaera

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

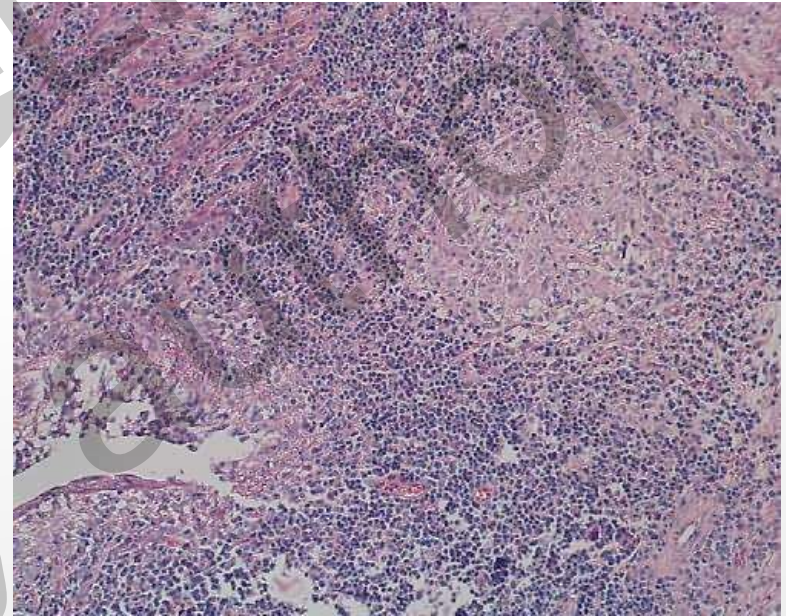
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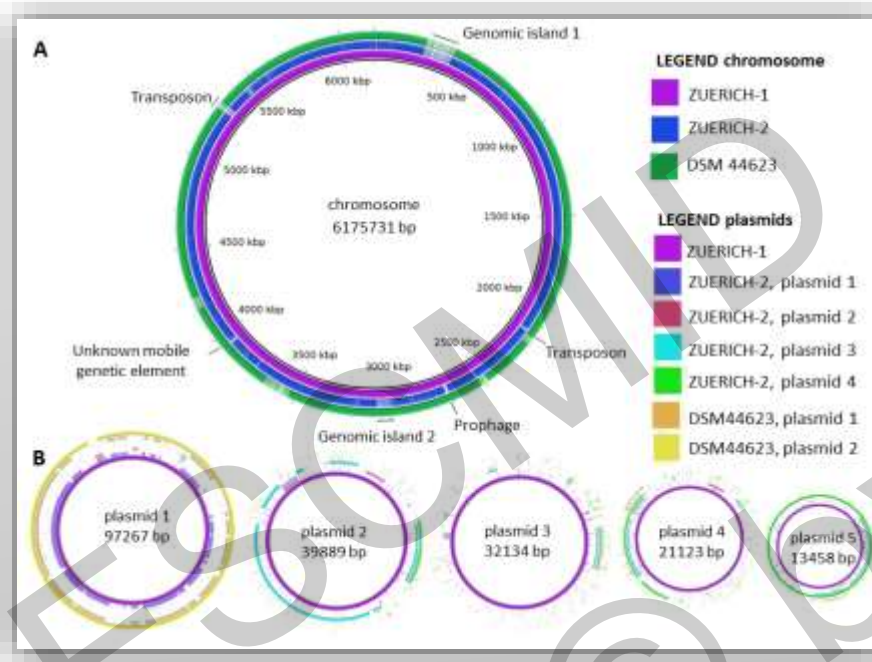
Pancytopenia, renal function deteriorating

Bone marrow and kidney with non-caseating granulomas

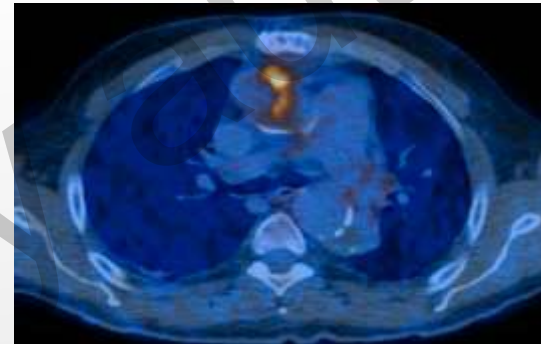


Heparin blood cultures, Cultures of bone marrow and kidney for mycobacteria

Alignment of genome sequences from *M. chimaera* strains ZUERICH-1, ZUERICH-2 and DSM 44623.



ZUERICH-1 versus ZUERICH-2: largely different 276 Kb chromosomal DNA (two large genomic islands, one prophage, and several complex transposons on the bacterial chromosome). Five plasmids.



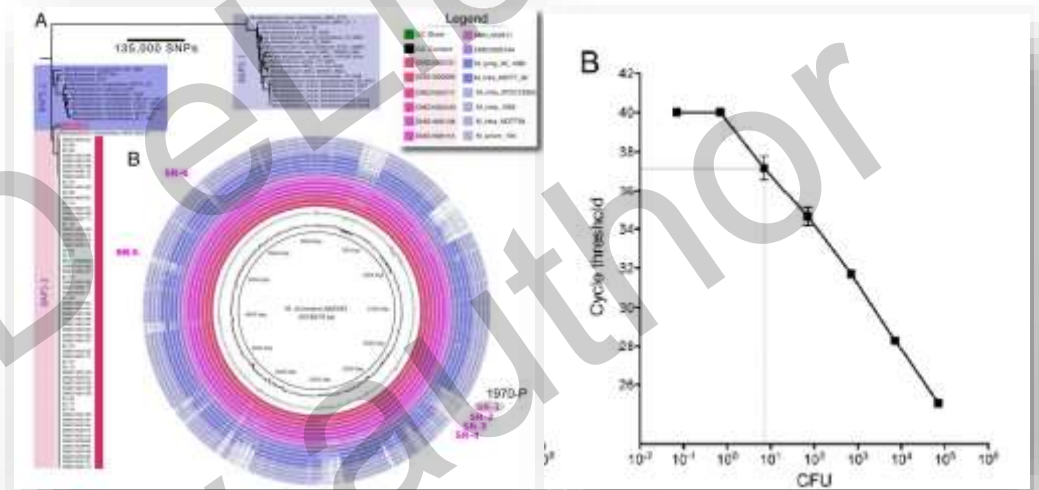
VASGRA
Vascular Graft Cohort Study

Improvement of diagnostic procedures in the near future?



Culture based techniques

BD BACTEC™ Myco/F Lytic



6 DNA regions present only in *M. chimaera*.

31 TaqMan qPCR assay for *M. chimaera*

Detection limit: 100 CFU/mL in whole blood

Action points for clinicians/ hospitals



Scope of the problem

Risk assessment

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Clinical management

Treatment for „clonal disease“: Macrolide + companion drugs

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.

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

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

Anti-TB drugs for MAC/ *Mycobacterium chimaera*

Clarithromycin (Never use as single agent therapy!)

- Mainstay of therapy
- Potential advantage: increased concentration in phagocytes and tissues
- MICs in the range of peak achievable serum levels (1–4 mg/ml)

Rifabutin

- Does not improve efficacy when added to a macrolide/ ethambutol
- Decreases the development of macrolide resistance

Ethambutol

- Decreases the development of macrolide resistance

Other drugs parenteral Amikacin (1-2 month of therapy), Moxifloxacin, others

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

Therapeutic drug monitoring

- No strong case

Multidrug regimens associated with adverse events/side effects

Clarithromycin

- Gastrointestinal, Toxicity dose and serum-level related

Ethambutol

- Ocular dose related toxicity, ophthalmological monitoring needed!

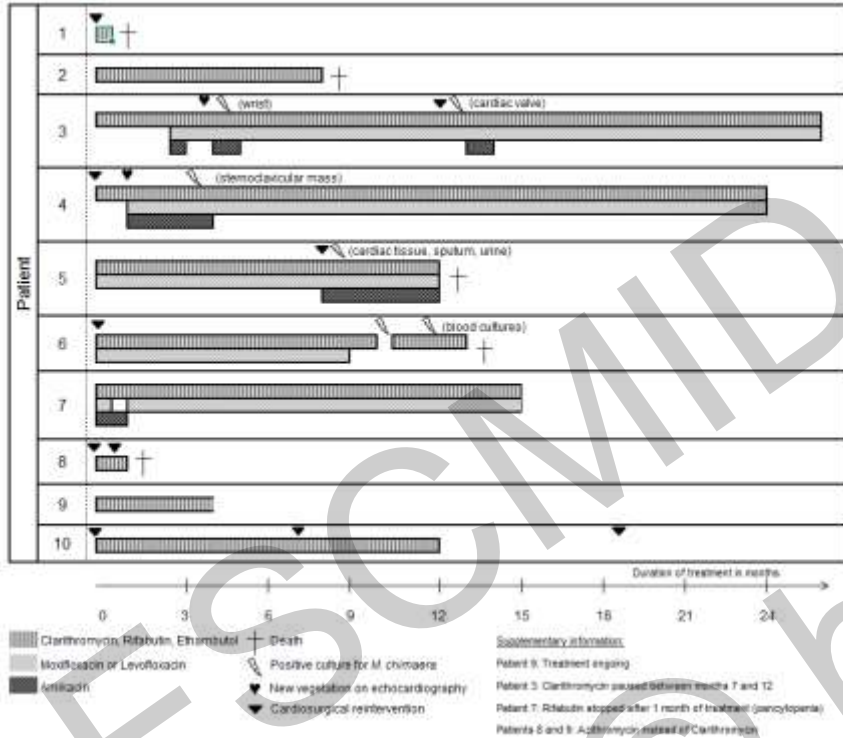
Rifabutin

- Gastrointestinal, Uveitis, Polyarthralgia, fever, Fever, white blood cell count
- Toxicity dose-related

Amikacin

- Renal and Oto-toxicity

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

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%)

Surgical debulking/ redo surgery due to biofilm formation



61 year old men: Redo surgery

History of mitral annuloplasty ring 2009

Therapy refractory course of an arthritis
of the left wrist under therapy with methotrexate
CRP 7.8 mg/L, Lc 4.39 G/L

Bone biopsy: microscopical acid fast bacilli

Culture: *Mycobacterium chimaera*

TEE: endocarditis of annuloplasty ring



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

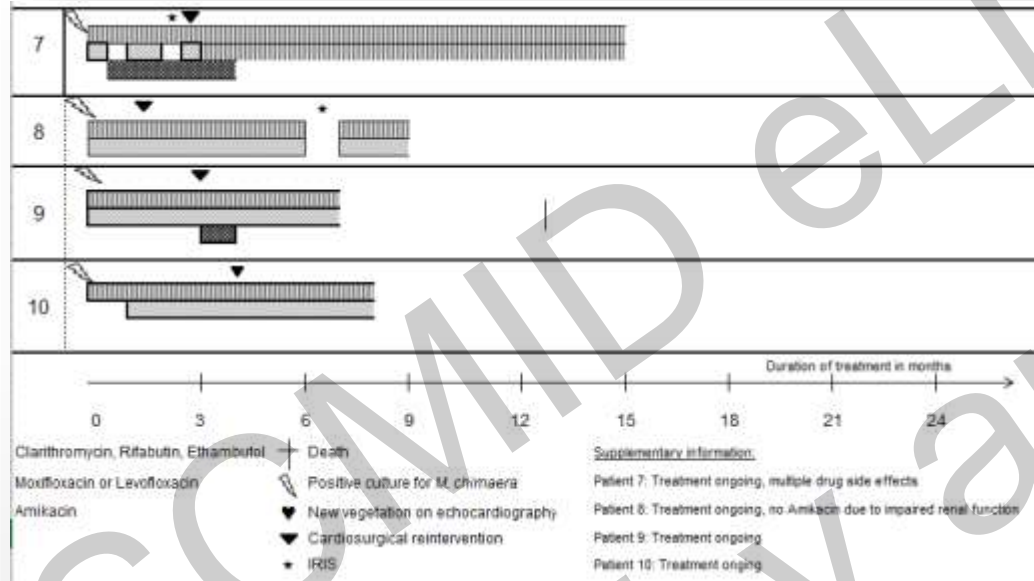
Chronic phase:

Tuberculostatic
treatment

Goal:

Treatment, hindrance of
new dissemination

«New» Swiss cases



No positive *M. chimaera* cultures after redo surgery

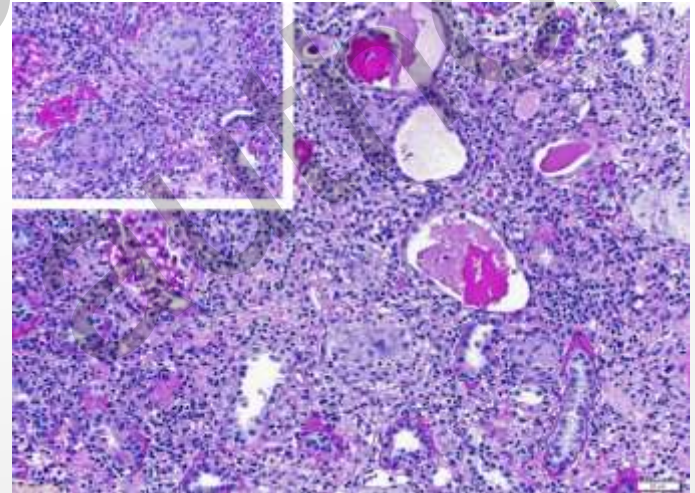
- Latency: 28 month
- Follow up time: 10.5 months

Redo-Operation: 3 month after diagnosis

Immune reconstitution inflammatory syndrome

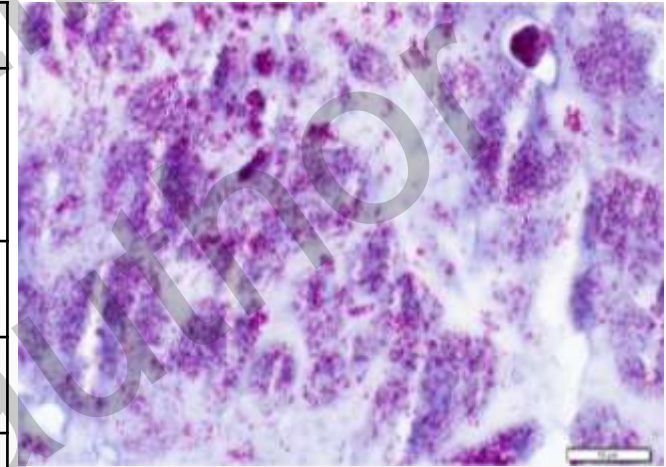
- Abscess formation of lymphnodes, ovar, spleen, prostate, bone
- Deteriorating renal function
- Worsening pancytopenia
- Cerebral vasculitis
- Progressive Chorioretinitis (?)

- Addition of 1 mg/kg body weight steroids



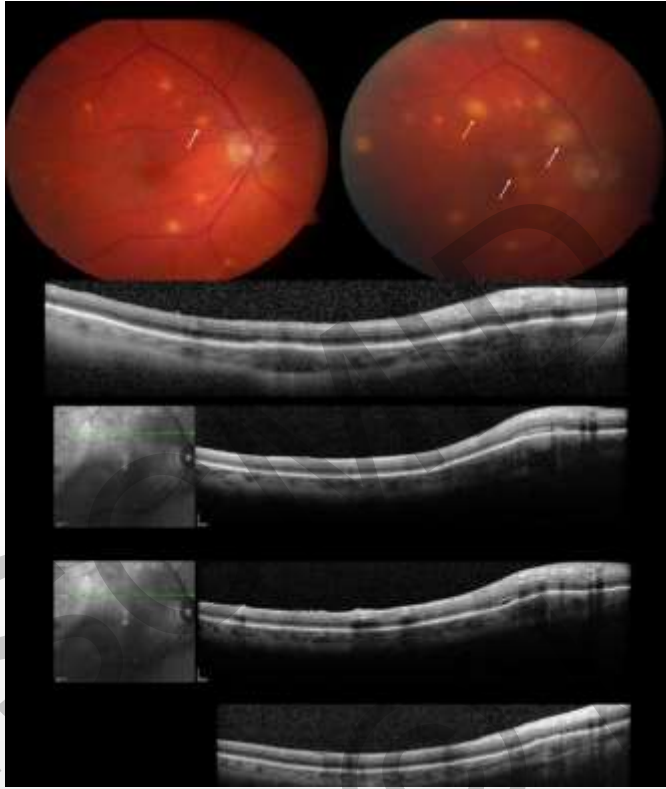
Outcome European patients revisited...

	Total patients	Death	Cure
Antibiotics Removal of prosthetic material	15 (100%)	5 (33%)	4 (26%)
Antibiotics only	4 (100%)	4 (100%)	0 (0%)
No antibiotics	1 (0%)	0 (0%)	0 (0%)
Overall	20 (100%)	9 (45)	4 (20%)



Acid fast stain from resected
composite aortic graft:
Culture: *M. chimaera*

Ocular manifestations: good indicators of disease control



Challenging treatment issues for the clinician

- 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?
- Is stopping of antimicrobial therapy feasible?

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
- Contact: barbara.hasse@usz.ch