Clinical management of *Mycobacterium chimaera* infection

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Treating physicians/ patients/ relatives
Disclosure: Evidence level low

- Systematic reviews
- Randomized controlled trials
- Cohort studies
- Case reports
- Expert opinion

Sackett DL. How to practice and teach EBM. Churchill Livingstone 2000
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• If withdrawn capacity of life-saving cardiac surgery affected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
Audit/ Feedback
- Multidisciplinary approach
- Consultant involvement
- Translational research
- Biofilm, NGS etc

Processes
- Infection prevention
- Diagnostics
- TDM
- Management side effects

Patient

Surveillance
- Screening
- Antibiograms
- Outcomes

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 abcess
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 detoriating
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
Risk assessment
Screening
Diagnosis and clinical presentation
Clinical management
The risk of getting the infection is low

**Our hospital**
1:500 cases

**UK**
0.39 cases per 10,000 PY

Chand et al. Clin Inf Dis 2017
The stochastic phenomenon of getting the infection

Mycobacterium chimaera
- Strain characteristics
- Contamination of HCU
- Biofilm persistence

HCU related
- Type of HCU (Stöckert 3T, Maquet, others)
- Maintenance of HCU
- Desinfection measures of HCU

Hazard

Heart surgery
- Duration of operation/ extracorporeal circulation
- Implantation of foreign material yes/no
- CABG on pump yes/no
- Perioperative complications

Operation room
- HCU in the OR or outside
- Distance of HCU from OR table
- Fan of HCU directs to OR table yes/no
- OR ventilation system

Patient related
- Immunosupression yes/no
- Genetic traits/ defects?
- Comorbidities

M. chimaera infection

Adapted from: https://en.wikipedia.org/wiki/Swiss_cheese_model
Association with cardiovascular implants

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

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 (?)

Kohler Ph et al. EHJ 2015, Haller S et al., Eurosurveillance 2016
Chand M et al. Clin Inf Dis 2017
82 year old men: No disseminated case

COPD, Coronary artery bypass surgery 2013
Presentation: Fever, weight loss, fatigue
Diagnosis: Perityphlitic abcess
Treatment: piperacillin/ tazobactam

Sputum: *Mycobacterium chimaera*

ON/OFF pump CABG
Action points for clinicians/ hospitals

Scope of the problem
Risk assessment
**Screening**
Diagnosis and clinical presentation
Clinical management
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»

- Recommended
  - Prosthetic valve endocarditis
  - Aortic graft infection
  - Fever of unknown origin
  - Sarcoidosis
  - Vasculitis
  - Systemic disease of unknown cause

- Recommended
  - Heart transplantation
  - Ventricular assist device

- Recommended
  - Asymptomatic

- Not recommended

n=127
n=62
n=10

Swiss Chimaera Collaborative Jan 2017
**Mycobacterium chimaera: The ethical duty to disclose the minimal risk of infection to exposed patients**

Information of 17,000 patients
- 2 patients referred for testing

Possibility of litigation
- Disclosure of the risk of *M. chimaera* infection to patients?
Action points for clinicians/ hospitals

Scope of the problem
Risk assessment
Screening
**Diagnosis and clinical presentation**
Clinical management
Challenges in diagnosis

- 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 manifestations.

- Chorioretinitis
- Pancytopenia
- Hepatitis
- Osteomyelitis
- Cerebral vasculitis
- Pneumonitis
- Splenomegaly
- Nephritis

Kohler et al. European Heart Journal 2015
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“

<table>
<thead>
<tr>
<th>Brucella spp</th>
<th>• Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxiella burnetii</td>
<td>• FUO</td>
</tr>
<tr>
<td>Bartonella spp</td>
<td>• Vasculitis</td>
</tr>
<tr>
<td>Tropheryma whipplei</td>
<td>Culture negative PVE and PVGI</td>
</tr>
<tr>
<td>Mycoplasma spp</td>
<td>• False detection as MAC/ M. intracellulare</td>
</tr>
<tr>
<td>Legionella spp</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium chimaera</td>
<td></td>
</tr>
</tbody>
</table>
66 year old man with sarcoidosis: your diagnostic steps?

History of composite graft operation
Fatigue and weight loss
Pancytopenia, renal function detoriating
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 ZURICH-2: largely different 276 Kb chromosomal DNA (two large genomic islands, one prophage, and several complex transposons on the bacterial chromosome). Five plasmids.
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
- Screening
- Diagnosis and clinical presentation

Clinical management
Treatment for „clonal disease“: Macrolide + companion drugs

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>MIC INH Mikrodil. day 7 [mg/L]</th>
<th>MIC INH Mikrodil. day 14 [mg/L]</th>
<th>MIC INH Mikrodil. day 21 [mg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>0.0625-0.25</td>
<td>0.5-1</td>
<td>2</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.015</td>
<td>0.061-0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>0.5-1</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin</td>
<td>2-4</td>
<td>2-4</td>
<td>4</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>0.25-1</td>
<td>0.5-1</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Dalamanid</td>
<td>1</td>
<td>2-4</td>
<td>4-8</td>
</tr>
<tr>
<td>Bedaquilin</td>
<td>&lt;0.015</td>
<td>0.03</td>
<td>0.03-0.06</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.5</td>
<td>&lt;0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Imipenem</td>
<td>8</td>
<td>32</td>
<td>128</td>
</tr>
<tr>
<td>Meropenem</td>
<td>4-8</td>
<td>8-16</td>
<td>32</td>
</tr>
<tr>
<td>Meropenem and Clavulanic acid</td>
<td>&lt;0.5</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Amoxicillin and Clavulanic acid</td>
<td>0.5-2</td>
<td>4-8</td>
<td>16-32</td>
</tr>
<tr>
<td>Sutezolid</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>US experience</th>
<th></th>
<th>European experience</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Deaths</td>
<td>Patients</td>
<td>Deaths</td>
</tr>
<tr>
<td>Antibiotics and removal of prosthetic material</td>
<td>6 (100%)</td>
<td>2 (33%)</td>
<td>8 (100%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Antibiotics only</td>
<td>14 (100%)</td>
<td>6 (43%)</td>
<td>2 (100%)</td>
<td>2 (66%)</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>4 (100%)</td>
<td>3 (75%)</td>
<td>0 (100%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Overall</td>
<td>24 (100%)</td>
<td>11 (46)</td>
<td>10 (100%)</td>
<td>6 (60%)</td>
</tr>
</tbody>
</table>

Appenheimer A, Whitener C et al. ID Week 2016
Kohler et al. European Heart Journal 2015
Surgical debulking/ redo surgery due to biofilm formation

In collaboration with Carlotta Fabbri, Leo Eberl, Institute of Plant biology, UZH
Kyrill Feldmann, Department of Materials, Soft materials, ETH Zürich
61 year old men: Redo surgery

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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

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

No positive M. chimaera cultures after redo surgery

Redo-Operation: 3 month after diagnosis

Stefan Erb, Peter Graber, Andreas Widmer, personal communications
Immune reconstitution inflammatory syndrome

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

- Addition of 1 mg/kg body weight steroids
Outcome European patients revisited...

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total patients</th>
<th>Death</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics Removal of prosthetic material</td>
<td>15 (100%)</td>
<td>5 (33%)</td>
<td>4 (26%)</td>
</tr>
<tr>
<td>Antibiotics only</td>
<td>4 (100%)</td>
<td>4 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>1 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Overall</td>
<td>20 (100%)</td>
<td>9 (45)</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>

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

Erb et al, Swiss Medical Forum 2017
With courtesy of Jakko von Ingen (NL), Dirk Wagner (D)
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