Non-tuberculous Mycobacteria from Heater Cooler Devices: A Global Outbreak

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Disclosure: Research funding from bioMérieux
• 60 yo male with hypertension
• Aortic dissection in early 2013
  • Repair with aortic graft
• Well until late 2014:
  • Weight loss (60 lbs total)
  • Fatigue, fevers, & night sweats
• Massive hepatosplenomegaly
• ↑ LFTs, pancytopenia
AFB Blood Culture Turns +

DNA probe + for *Mycobacterium avium* complex (MAC)
Molecular ID eventually reveals: *M. chimaera*

Mycobacterium avium Complex (MAC)

- Slow-growing, ubiquitous in environment
  - Surface water, tap water, and soil
- **Low virulence**, opportunistic pathogens
  - Disseminated disease described with extreme immune compromise (AIDS)
  - Chronic lung disease, airway abnormalities
- Detection challenging (2-8 weeks to grow)

*How did this otherwise healthy patient acquire disseminated MAC disease?*
Invasive *M. chimaera* infection in 6 patients

All the case patients had cardiac implants

Time from surgery to diagnosis: 1.7-3.6 years

Investigation of water sources revealed:

- Water in **heater-cooler devices** grew *M. chimaera*
  - LivaNova (formerly Sorin) Stockert 3T
- Air samples grew the outbreak strain when units ran
- Water, air and patient samples matched by RAPD-PCR
What is a Heater-Cooler Device (HCD), and how could it serve as a source of bio-aerosols?
Although water from heater-cooler never contacts patients directly, the circuit is not airtight (or watertight), so the ventilation fan can aerosolize contaminated water from the circuit.
Peeking under the hood…

Figure 5. Use of a smoke tracer to visualize air flow path as it is extracted from the pumps/gaps associated with the water tanks and exiting the heater-cooler unit via the rear fan.

Contamination of the operative field

HCU fan facing away from operative field

HCU fan facing operative field

https://www.youtube.com/watch?v=YZ41aLoHrhQ
Outbreak investigation at Wellspan York: CDC and Pennsylvania DOH

• Case control study performed
  – 11 cases, 48 controls
  – **Cases**: extra-pulmonary NTM up to 3.5 years after cardiothoracic surgical procedure
  – **Controls**: no + cx after CT surgery

• **Exposure to HCD** was a risk factor
• Exposure > 2 hrs to HCD (OR = 16.5 [3.2-84])
• Molecular typing linked patient isolates

Why *Mycobacterium chimaera*?

1. Because LivaNova 3Ts may have arrived already contaminated with *M. chimaera*

2. Because *M. chimaera* (and other NTM) are perfectly suited to survive in, and aerosolize from, water circuits
Evidence for Contamination at the Source

Mycobacterium chimaera-positive samples from environmental investigations at the manufacturing site of new HCUs and of used HCUs from at the manufacturer’s service centre, July 2014 to June 2015

<table>
<thead>
<tr>
<th>Date</th>
<th>Type of sample</th>
<th>Source of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 Jul 2014</td>
<td>Water (100 mL)</td>
<td>Used HCU from Switzerland</td>
</tr>
<tr>
<td>29 Jul 2014</td>
<td>Water (100 mL)</td>
<td>New HCU from manufacturing site</td>
</tr>
<tr>
<td>5 Aug 2014</td>
<td>Water (100 mL)</td>
<td>New HCU from manufacturing site</td>
</tr>
<tr>
<td>11 Aug 2014</td>
<td>Water (100 mL)</td>
<td>New HCU from manufacturing site</td>
</tr>
<tr>
<td>19 Feb 2015</td>
<td>Water (100 mL)</td>
<td>Used HCU from the Netherlands</td>
</tr>
<tr>
<td>10 Jun 2015</td>
<td>Water (volume not specified)</td>
<td>Sample taken in pump assembly area at the manufacturing site</td>
</tr>
</tbody>
</table>

HCU: heater-cooler unit.

“HCDs....may have had environmental mycobacteria presence in the unit at the time of delivery.”

Molecular epidemiology:
A common source outbreak

• Whole genome sequencing reveals isolates from multiple continents to be closely related:
  – 3T HCD and patient isolates from UK, Europe, US, AU/NZ
    • van Ingen J, et al. Lancet Infect Dis 2017 (ePub)
    • Perkins KM, et al. MMWR 2016;65:1117-18

“We find it likely that most [LivaNova] Sorin 3T HCDs made in the past 8-10 years potentially are contaminated by the same M. chimaera strain”
WGS of 250 isolates worldwide

“HCD contamination with *M. chimaera* at the LivaNova factory seems a likely source for...surgery-related severe *M. chimaera* infections”
Global outbreak of HCD-associated *M. chimaera*

- Switzerland
- Germany
- France
- Spain
- Netherlands
- United Kingdom
- Hong Kong
- Australia
- Canada

Worldwide case count unknown, >110
M. chimaera aerosolization in the OR: Pathogenesis of disseminated infection

• Most patients to date with disseminated infections have implants (valves, vascular grafts, LVADs)
• High inoculum (long bypass time, direction of exhaust, OR air handling) results in contamination of implant, leads to biofilm formation on an intravascular device
• Chronic granulomatous inflammatory response to near-continuous bacteremia with a low virulence organism that is otherwise easily contained
MAC Outer Membrane Favors Persistence in Water Systems

• Lipid-rich hydrophobic barrier
• Resistant to common disinfectants
  – Chlorine, chloramine, ozone
• 1,000 times more resistant than industry standard for disinfection (E. coli)
  – 5 seconds vs. 2 hours at 1 ppm chlorine
• Form thick biofilms, enhance resistance
  – 10,000 CFU/cm2 in biofilm

MAC Hydrophobicity: Role in Aerosolization

• Concentrate on surface of air bubbles in water columns
• Aerosolization as bubbles reach surface
• MAC concentration in ejected droplets is 1,000-10,000 X higher than in water

Clinical manifestations

- Surgical wound infection
  - SSI, sternal osteomyelitis, mediastinitis, abscess
- Prosthetic valve endocarditis
- Vascular graft infection
- LVAD infection
- Dissemination:
  - Bone marrow (cytopenias common)
  - Splenomegaly
  - Hepatitis
  - Nephritis
  - Arthritis and osteomyelitis (spine, discitis)
  - Chorioretinitis
  - Pneumonitis
  - Myocarditis
Disseminated *M. chimaera*: Device Associated

Current approach to therapy includes **multiple drug treatment** (macrolide, ethambutol, rifamycin, +/- amikacin, +/- moxifloxacin), and **removal of involved devices** (valve, graft) if possible.

# M. chimaera clinical experience

52 cases from 3 case series (US, UK, EU)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>52</td>
</tr>
<tr>
<td>Earliest sentinel surgery</td>
<td>2008</td>
</tr>
<tr>
<td>Male</td>
<td>83%</td>
</tr>
<tr>
<td>Age, y (mean, range)</td>
<td>60 (1-83)</td>
</tr>
<tr>
<td>Prosthetic cardiovascular material</td>
<td>90%</td>
</tr>
<tr>
<td>Duration from surgery to symptom onset in months, mean (range)</td>
<td>17 (1-72)</td>
</tr>
<tr>
<td>Crude mortality at time of publication or presentation of cases</td>
<td>48%</td>
</tr>
</tbody>
</table>

Appenheimer AB et al. IDWeek 2016, #2392, October 29, 2016.
Surgical procedure

- Prosthetic Valve/Ring
- Aortic graft
- LVAD
- Valve + graft
- Heart transplant
- CABG

Localized, sternal wound/mediastinitis/pleural

Appenheimer AB et al. IDWeek 2016, #2392, October 29, 2016.
Clinical presentation

<table>
<thead>
<tr>
<th>Presumed source</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valve</td>
<td>32</td>
</tr>
<tr>
<td>Aortic graft</td>
<td>9</td>
</tr>
<tr>
<td>LVAD</td>
<td>6</td>
</tr>
<tr>
<td>Sternal wound</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>90</td>
</tr>
<tr>
<td>Fever</td>
<td>75</td>
</tr>
<tr>
<td>Sweats</td>
<td>60</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>60</td>
</tr>
<tr>
<td>Weight loss</td>
<td>60</td>
</tr>
<tr>
<td>Cough</td>
<td>50</td>
</tr>
</tbody>
</table>

• **Sites of dissemination**: liver, spleen, bone marrow, kidney, eye (chorioretinitis), spine (osteomyelitis), joints, pleural space, psoas muscle, myocardium

• **Histopathology**: non-caseating granulomas, rarely AFB smear positive

Appenheimer AB et al. IDWeek 2016, #2392, October 29, 2016.
## Diagnosis (2 case series, 34 patients)

<table>
<thead>
<tr>
<th>Sites of positive culture</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>14</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac tissue or device</td>
<td>5</td>
</tr>
<tr>
<td>Sternal wound</td>
<td>3</td>
</tr>
<tr>
<td>Pleural space</td>
<td>3</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
</tr>
<tr>
<td>Urine</td>
<td>2</td>
</tr>
<tr>
<td>LVAD pocket</td>
<td>1</td>
</tr>
</tbody>
</table>

- **PCR can be valuable in setting of negative cultures**
  - 7 of 10 cardiac tissue PCR + in Kohler series

Appenheimer AB et al. IDWeek 2016, #2392, October 29, 2016.
Diagnostic considerations

• If exposed and with unexplained symptoms:
  – Fatigue, fever, night sweats, weight loss, surgical site
  – Exam: ? HSM, surgical site, joint involvement, ophtho exam
  – Labs: CBC/diff, chem 7, LFTs, CRP, UA, AFB blood/other cx

• Cytopenias, elevated LFTs, AKI, chorioretinitis
  – Often seen at presentation with disseminated disease

• Cultures require mycobacterial lab expertise
  – Take several weeks to turn positive
  – ID as “MAC” by probe, few labs can do species ID
  – Culture blood (>=2 sets) and any involved site
  – “Screening” AFB blood cultures (asymptomatic) not indicated
Outcomes of invasive *M. chimaera*

- Case series to date: crude mortality 50%
- Among the remaining 50%:
  - Those with localized infections (e.g. sternal wound, mediastinal abscess) cured with I&D
  - Those with disseminated infection:
    - Unwell, tenuous, on medical treatment
    - In post surgical (device removal) monitoring period
  - More experience, follow up needed (registry)

Appenheimer AB et al. IDWeek 2016, #2392, October 29, 2016.
Are your patients at risk?

- Yes, if LivaNova (Sorin) 3T HCDs used anytime since….2008, 2010, 2012?
  - Assume HCDs are contaminated regardless of manufacture date or HCD culture results
  - Next steps:
    1. Find current cases
    2. Manage identified cases
    3. Prevent additional cases
Case finding
Assemble a team to coordinate:

• Development of line list of those exposed
  – Patient notification (closed loop, call-in line)
  – Laboratory and EMR look-back
  – EMR alert (exposed + febrile/other illness)

• Provider notification, Media release

• Patient evaluation: diagnostic approach

https://www.cdc.gov/hai/outbreaks/heater-cooler.html
http://haicontroversies.blogspot.com/2016/11/the-m-chimaera-how-to-guide.html
Case finding

• Exposed patients with consistent syndrome:
  – Offered evaluation in a dedicated NTM clinic
    • Staffed by a physician’s assistant
    • Directed by an ID physician
    • Checklist developed with input from ID and external experts to trigger the need for cultures
      – Included symptoms, signs, lab results (elevated LFTs, pancytopenia), prior workup
  – Instructions provided for pts to take to local PCP
Case finding results: University of Iowa

- First case detected January 2016
- 1,500 patients potentially exposed
- ~150 symptomatic patients underwent evaluation in “NTM clinic”
  - no additional cases diagnosed from this clinic
- 6 *M. chimaera* cases identified to date
Case finding: Challenges

- Many pts receive follow-up care locally, not at the center where they had surgery
- Symptoms are very nonspecific
  - fever, fatigue, arthralgias/myalgias
- Long incubation period
- Mycobacterial cultures are not routinely performed, but are required for diagnosis
Case finding: Challenges

• Mycobacteriology laboratory capacity
  – Our initial evaluation exceeded capacity of blood culture instrument, so we converted to manual Isolator method temporarily
  – For most labs, species-level ID (*M. chimaera*) and susceptibility testing is a send out

• Discuss with lab director!
Prevention: The Swiss Cheese Model

Schrieber and Sax. Curr Opin Infect Dis 2017
Prevention measures: HCD management

- Manufacturer cleaning/disinfection guidance
  - http://www.livanova.sorin.com/products/cardiac-surgery/perfusion/hlm/3t

- FDA and LivaNova recommend considering environmental cultures to monitor HCD
  - http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm466963.htm

- Few labs have expertise in NTM isolation
  - One center, same week, two labs ➔ opposite results

- Negative predictive value is unknown

- Sequential testing demonstrates variability

- Safest to consider all 3T HCDs contaminated
Can *M. chimaera* be eradicated from HCDs?

- Contamination of new, factory-direct units quickly detected
- Multiple cycles of decontamination fail to eliminate:
  - Daily water changes with filtered water and 100 mL 3% H$_2$O$_2$
  - Biweekly disinfection with bleach or peracetic acid + H$_2$O$_2$

A year in the life of a contaminated HCU…

M. chimaera

Total CFU

Mold counts

P. aeruginosa

“Degradation and breakdown of internal components”

Prevention measures:
Separation of HCD exhaust from OR air

Prevention measures:
Separation of HCD exhaust from OR air

Prevention measures:

“Wall water” system that eliminates need for HCD

Utilizes hot and cold water inputs and medical grade mixing valve to carefully regulate water temperature and delivery to the bypass system.

Built-in water filtration.

Watertight, no HCD, no fans.

Requires major capital investment for hospitals without hot and cold water supply in proximity to OR.

Matte GS, Sandora TJ, et al. SHEA Spring Meeting, 2017, St. Louis, MO.
LivaNova PLC (NASDAQ:LIVN) (together with its subsidiaries as "LivaNova" or the "Company"), a market-leading medical technology company, today announced the implementation of a device modification to its existing 3T Heater-Cooler devices in Western Europe. During the past fiscal quarter, LivaNova successfully completed verification and validation processes, which allowed the Company to obtain CE Mark for its 3T Heater-Cooler device modification. It began implementing upgrades in Europe and implementation will extend to other regions as local regulatory approvals are received. The modification, which is being implemented at no cost to customers, includes the installation of an internal sealing and vacuum system on existing devices. This addresses regulatory actions and is designed to mitigate the potential for Mycobacterium chimaera (M. chimaera) contamination in open-heart surgery patients.
Summary: Epidemiology

• Common source outbreak of *M. chimaera*
  – LivaNova 3T HCDs contaminated at manufacturing facility
  – Exposure to HCD exhaust air during surgery

• Extent of outbreak unknown at this time
  – Very long incubation/discovery period (> 6 years)
  – Clinical follow up often distant from exposure
  – Risk: if case detected, risk 1/100 -1/1,000

• Risk from other HCDs, other organisms?
Summary: Clinical Manifestations

- Challenging clinical syndrome:
  - Delayed presentation, protean manifestations
  - Diagnosis delayed: AFB culture/PCR required
  - Treatment of invasive/disseminated difficult
    - Multidrug medical therapy (3+ agents)
    - Surgical removal of prosthetic devices
  - Very high crude mortality rate (>=50%)
Summary: Hospital response

- Actively notify exposed patients via multiple means including media outlets
- Consider all LivaNova 3T HCDs contaminated
  - Culturing of HCDs of limited value
  - Follow manufacturer’s disinfection instructions
  - Decontamination approaches unreliable
- Most important means of risk mitigation is to separate the HCD bioaerosol from the patient
Future directions

• Re-designed heater-cooler systems
• Greater infection control scrutiny of devices
  – e.g. scopes, HCDs, ability to operate safely
• Improved diagnostics (e.g. NGS, other)
• Registry for *M. chimaera* cases
  – Diagnosis, treatment, outcomes