

Epidemiology of a Global Outbreak Linked to Heater Cooler Devices

Daniel Diekema, MD, D(ABMM)

Director, Division of Infectious Diseases



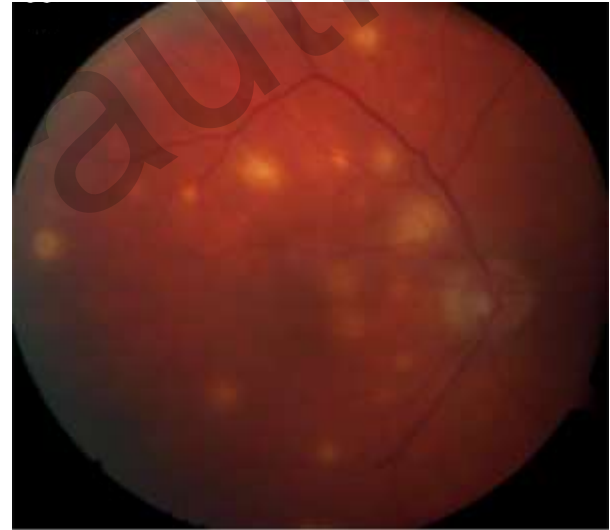
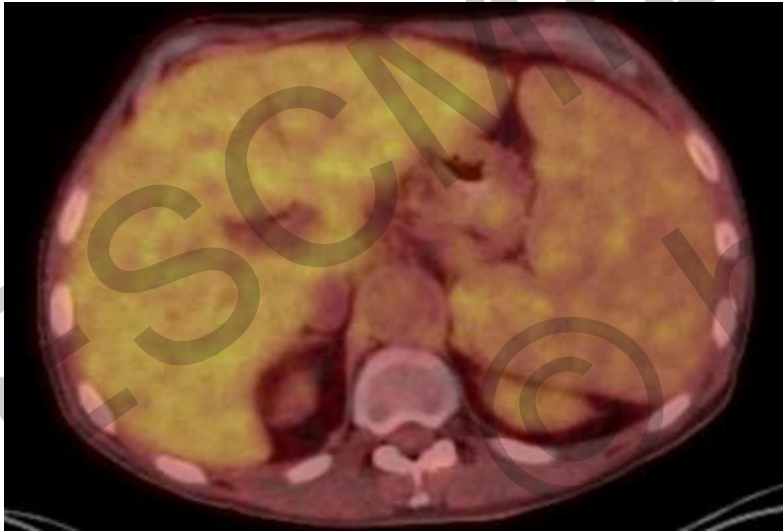
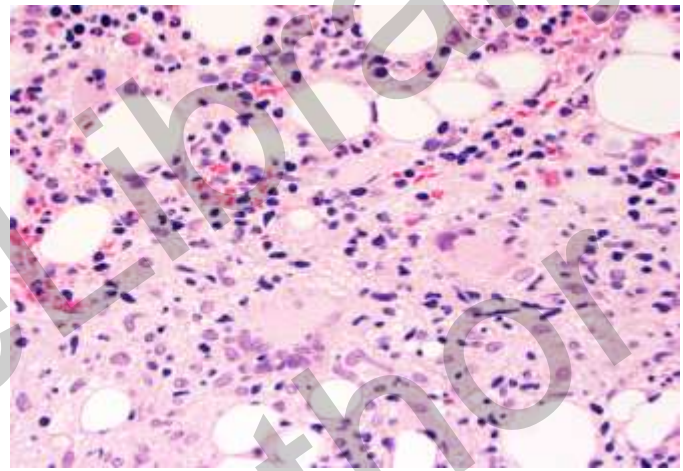
UNIVERSITY OF IOWA
HOSPITALS & CLINICS

University of Iowa Health Care

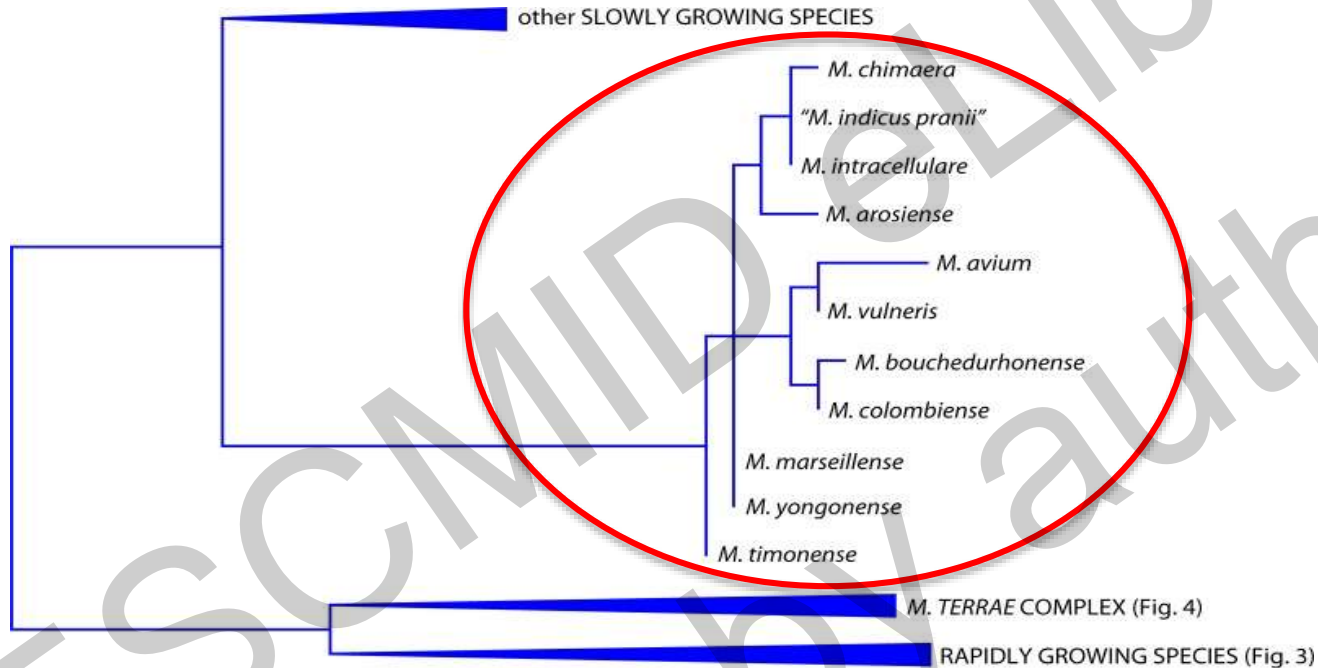
Disclosure: Research funding from bioMérieux



- 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?

Prolonged Outbreak of *Mycobacterium chimaera* Infection After Open-Chest Heart Surgery

Hugo Sax,^{1,a} Guido Bloemberg,^{2,a} Barbara Hasse,^{1,a} Rami Sommerstein,¹ Philipp Kohler,¹ Yvonne Achermann,¹ Matthias Rössle,³ Volkmar Falk,⁴ Stefan P. Kuster,¹ Erik C. Böttger,^{2,b} and Rainer Weber^{1,b}

¹Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, ²Institute of Medical Microbiology, National Centre for Mycobacteria, University of Zurich, ³Institute of Surgical Pathology, and ⁴Division of Cardiac Surgery, University Hospital Zurich, Switzerland

- 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?

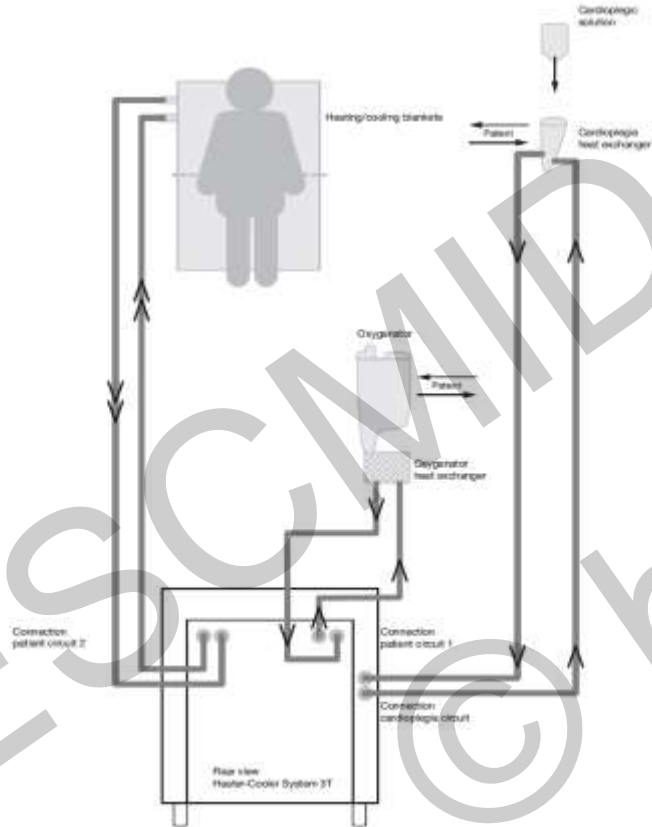
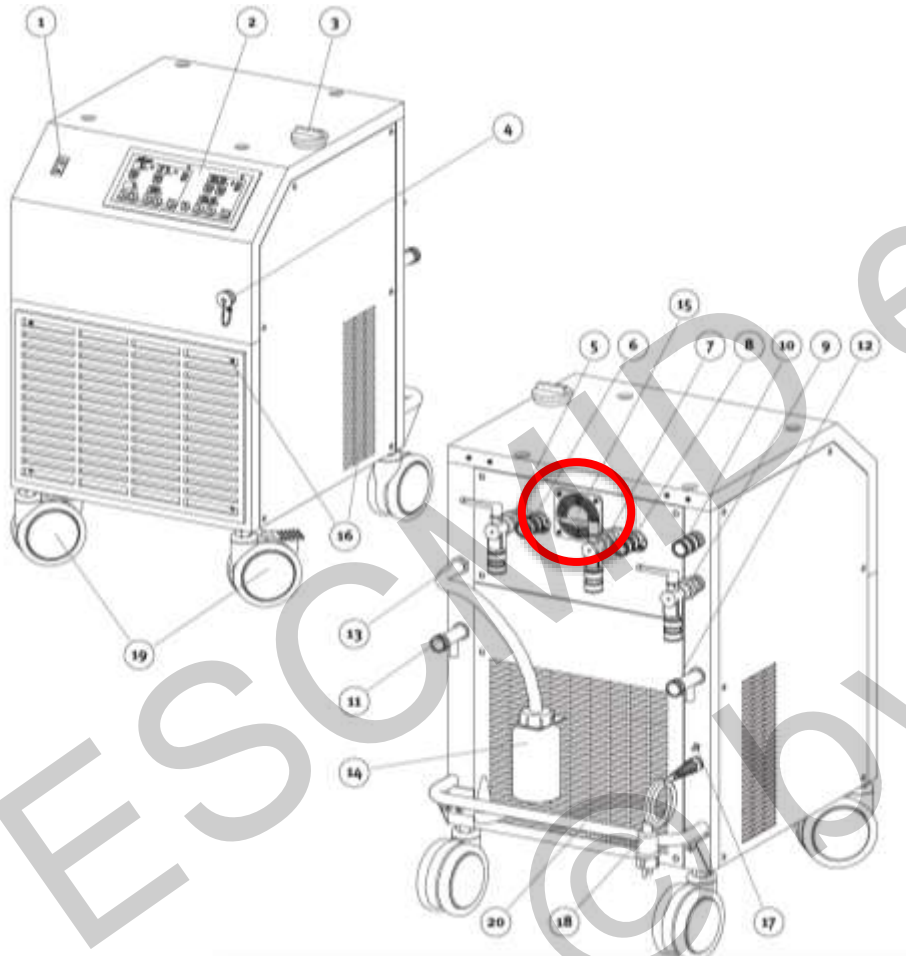


Fig. 7. Overview connecting additional devices





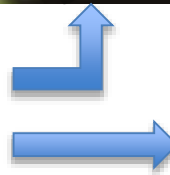
Although water from heater-cooler never contacts patients directly, the circuit is not airtight (or watertight), so the ventilation fan can aerosolize contaminated water from the circuit

Peeking under the hood...



Chand et al. Clin Infect Dis 2017;64:335-42.

Lyman, et al. Emerg Infect Dis 2017;23:796.

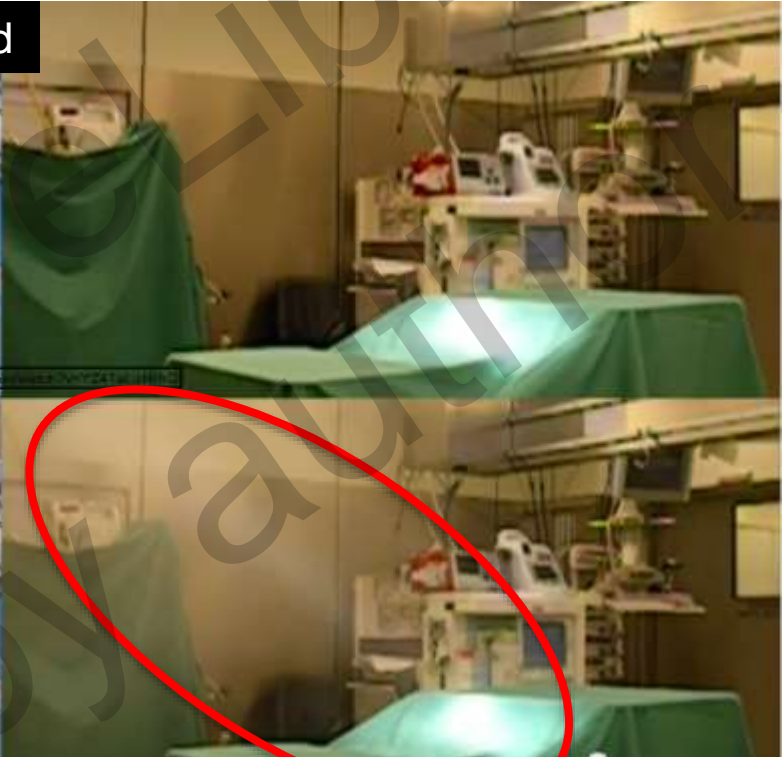


Contamination of the operative field

HCU fan facing away from operative field



HCU fan facing operative field



Sommerstein R, et al. EID 2016;22:1008-1013
<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

Lyman, et al. Emerg Infect Dis 2017;23:796.

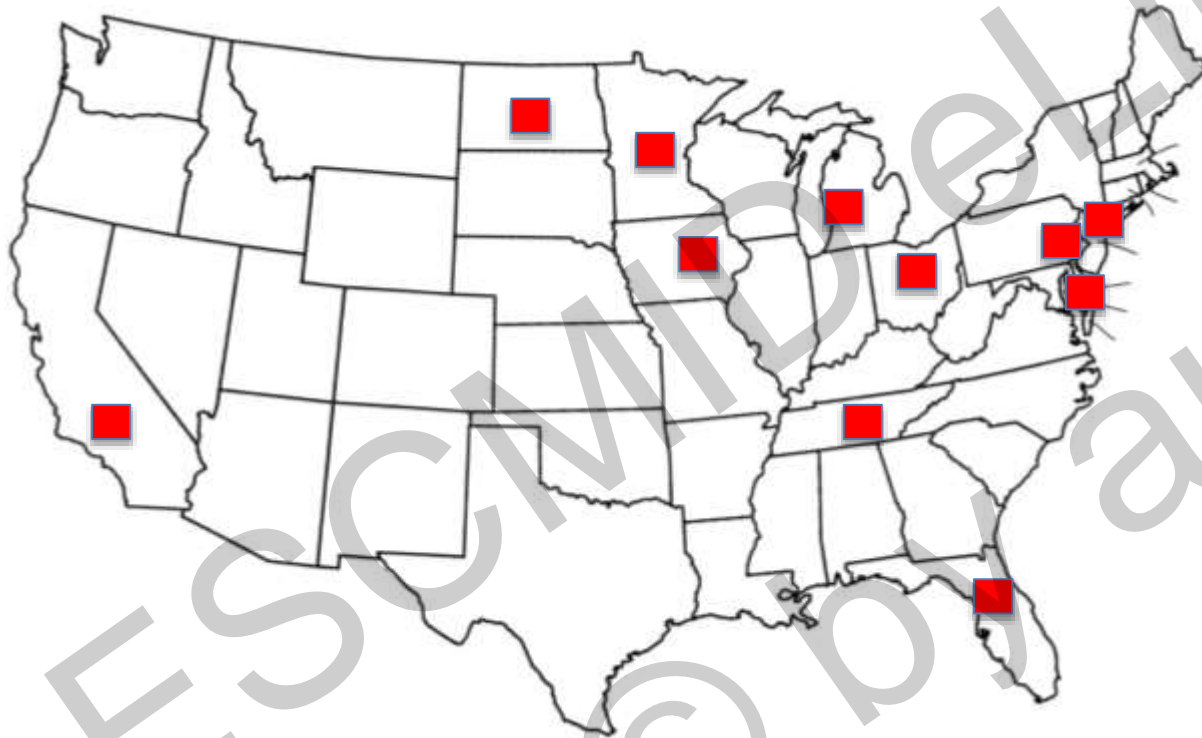
Molecular epidemiology:

A common source outbreak

- *M. chimaera* in water from pump assembly area
 - Haller S et al. Eurosurveillance 2016;21:17
- 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. ECCMID 2016, session E036
 - Svensson E, et al. Emerg Infect Dis 2017 (ePub)
 - Perkins KM, et al. MMWR 2016;65:1117-18
 - Williamson D, et al. N Engl J Med 2017;376:600-602

“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”

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

- All 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 seeding of the bloodstream by 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

Taylor, et al. Appl Environ Microbiol 2000;66:1702-5.
Steed, et a. Appl Environ Microbiol 2006;72:4007.

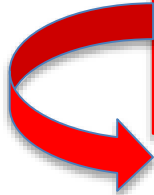
MAC Hydrophobicity: Role in Aerosolization

- 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



M. chimaera clinical experience

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

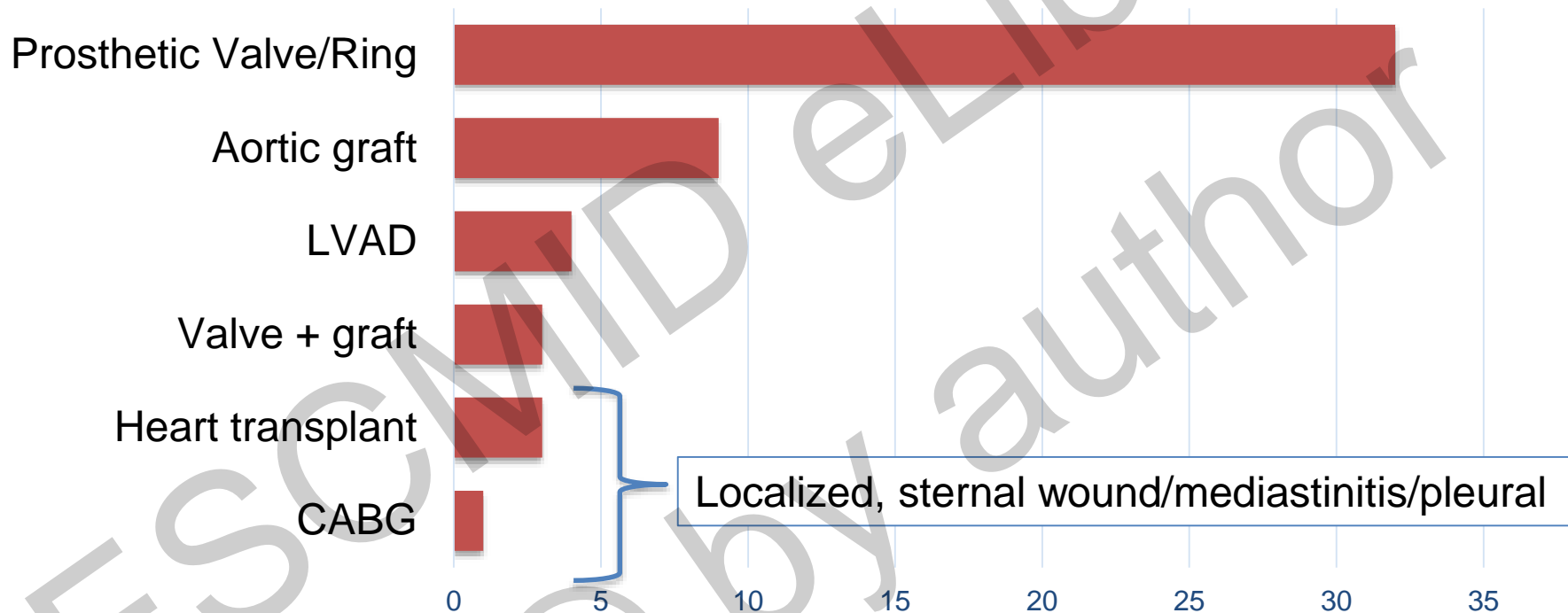
Patient Characteristics	Results
Total number of cases	52
Earliest sentinel surgery	2008
Male	83%
Age, y (mean, range)	60 (1-83)
Prosthetic cardiovascular material	90%
Duration from surgery to symptom onset in months, mean (range)	17 (1-72)
Crude mortality at time of publication or presentation of cases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

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

Chand M, et al. Clin Infect Dis 2017;64:335-42.

Kohler P, et al. European Heart Journal 2015;36:2745-53.

Surgical procedure



Appenheimer AB et al. IDWeek 2016, #2392, October 29, 2016.
Chand M, et al. Clin Infect Dis 2017;64:335-42.
Kohler P, et al. European Heart Journal 2015;36:2745-53.

Clinical presentation

Presumed source	N
Prosthetic valve	32
Aortic graft	9
LVAD	6
Sternal wound	5

Symptoms	%
Fatigue	90
Fever	75
Sweats	60
Dyspnea	60
Weight loss	60
Cough	50

- **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.

Chand M, et al. Clin Infect Dis 2017;64:335-42.

Kohler P, et al. European Heart Journal 2015;36:2745-53.

Diagnosis (2 case series, 34 patients)

Sites of positive culture	N
Blood	14
Bone marrow	5
Cardiac tissue or device	5
Sternal wound	3
Pleural space	3
Liver	2
Urine	2
LVAD pocket	1

- **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.
Kohler P, et al. European Heart Journal 2015;36:2745-53.

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

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:



• Find current cases

• Manage identified cases

• 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

<http://ecdc.europa.eu/en/publications/Publications/RRA-mycobacterium-chimaera-November-2016.pdf>

<https://www.cdc.gov/hai/outbreaks/heater-cooler.html>

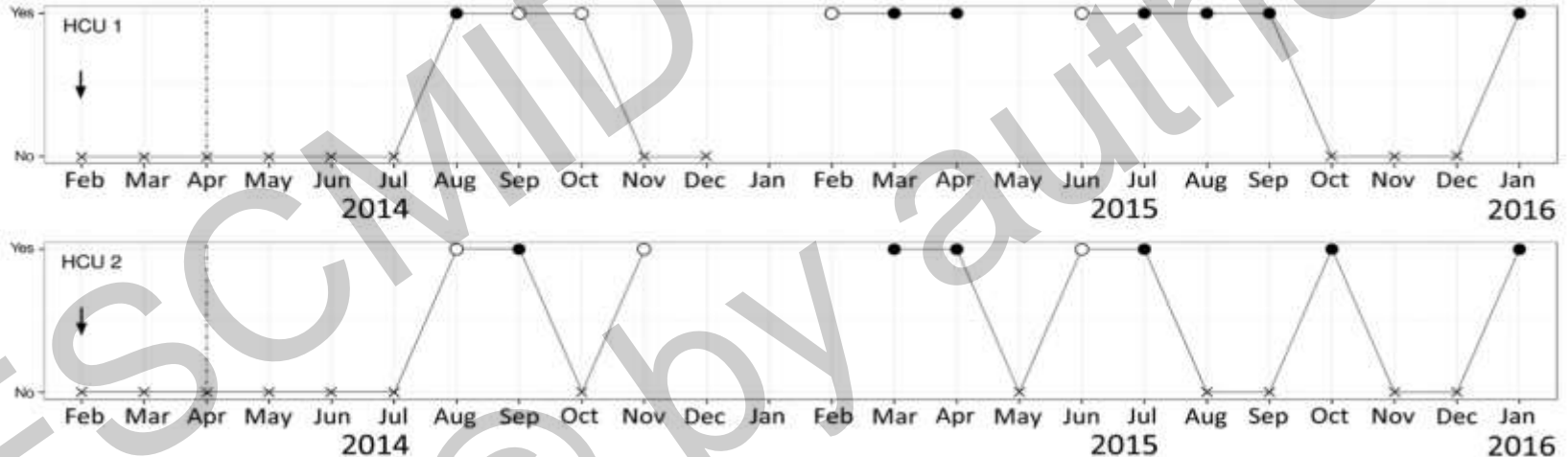
<http://haicontroversies.blogspot.com/2016/11/the-m-chimaera-how-to-guide.html>

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% H₂O₂
 - Biweekly disinfection with bleach or peracetic acid + H₂O₂



● *M. chimaera*
○ Other NTM

Schreiber PW et al. Emerg Infect Dis 2016;22:1830-3.
Garvey MI et al. J Hosp Infection 2016;93:229-34.
Gotting T et al. J Hosp Infection 2016;93:223-8.

Prevention measures:

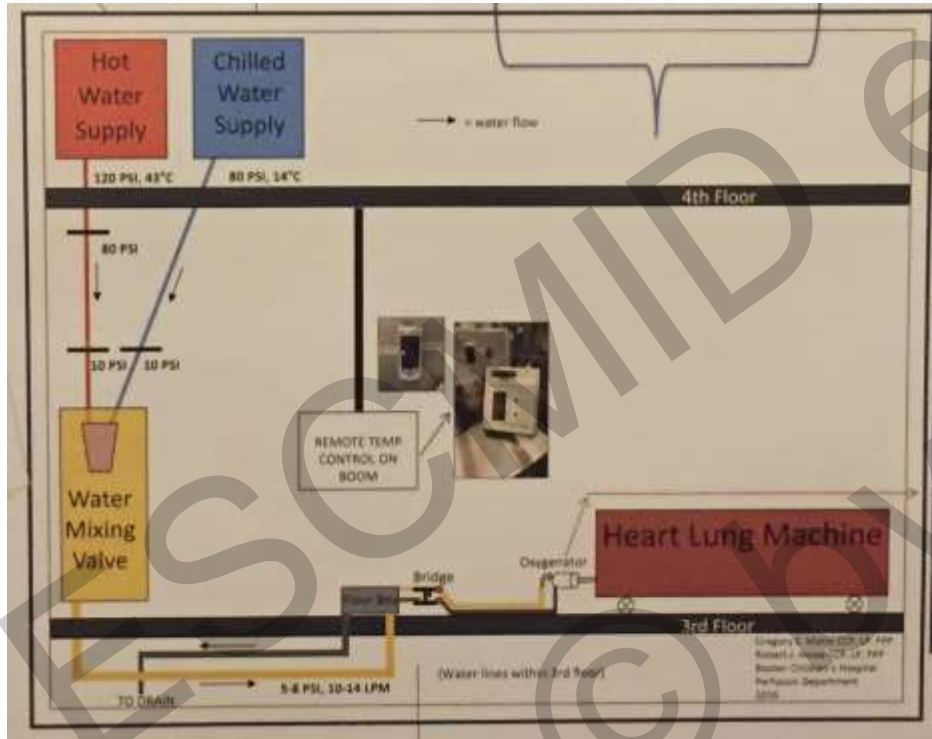
Separation of HCD exhaust from OR air



Schreiber PW et al. Emerg Infect Dis 2016;22:1830-3.
Marra A, et al. Clin Infect Dis 2017 (in press).

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.

Summary: Epidemiology

- Common source outbreak of *M. chimaera*
 - LivaNova 3T HCDs contaminated at manufacturing facility and shipped to hospitals globally
 - 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
 - Likely highly variable based upon HCD use practices
- Risk from other HCD models, other organisms not known

Summary: Clinical Manifestations

- Challenging clinical syndrome:
 - Delayed presentation, protean manifestations
 - Diagnosis delayed: AFB culture/PCR required
 - Treatment of invasive/disseminated difficult
 - Very high crude mortality rate ($\geq 50\%$)

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 not reliably effective
- Most important means of risk mitigation is to separate the HCD bioaerosol from the patient