

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

**Daniel Diekema, MD, D(ABMM)**

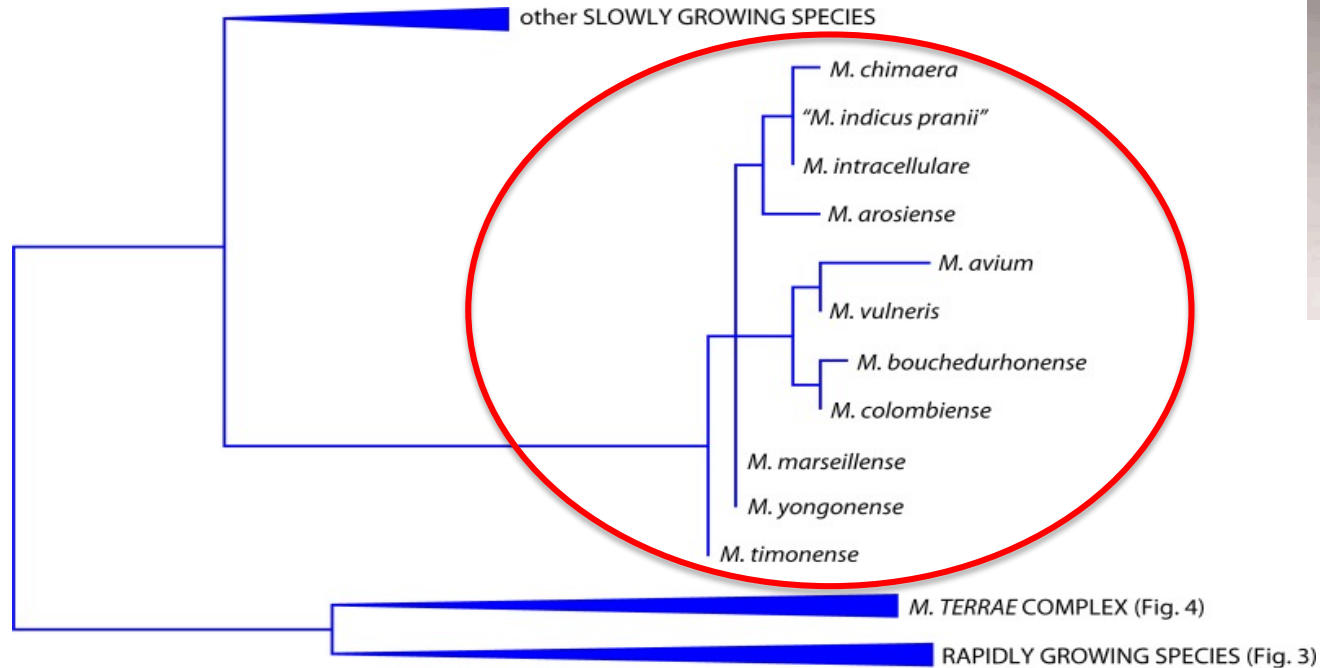
Director, Division of Infectious Diseases



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?*

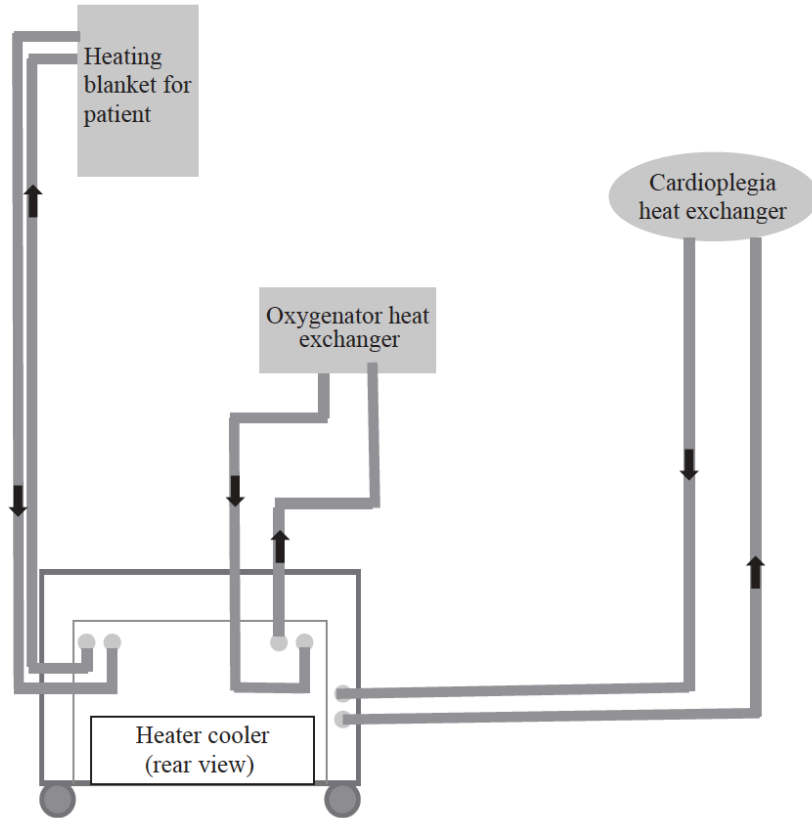
# Prolonged Outbreak of *Mycobacterium chimaera* Infection After Open-Chest Heart Surgery

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

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

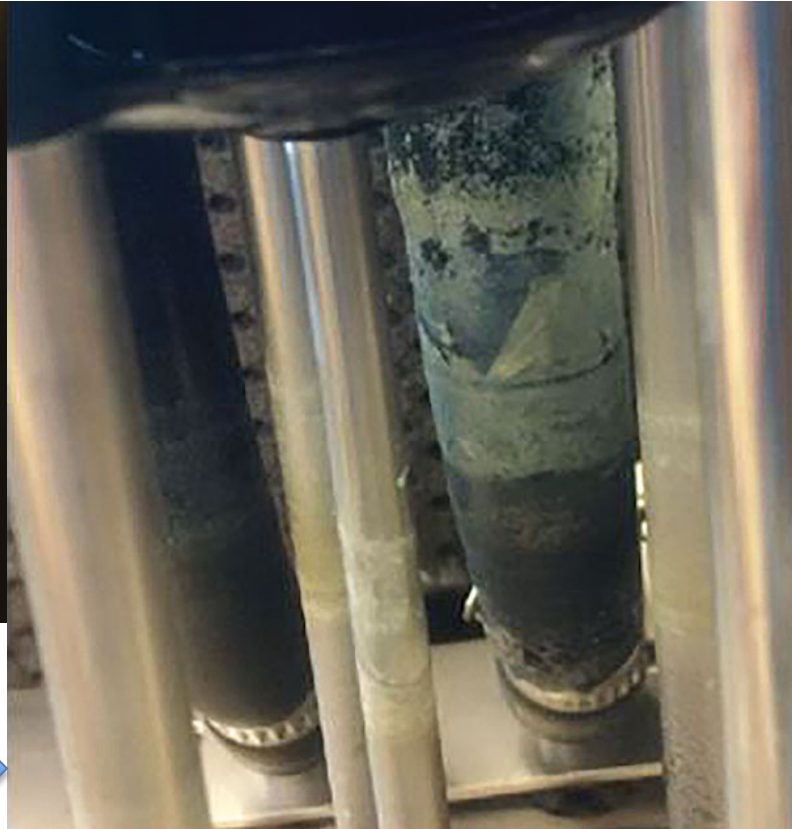
- Invasive *M. chimaera* infection in 6 patients
- All the case patients had cardiac implants
- Time from surgery to diagnosis: 1.7-3.6 years
- Investigation of water sources revealed:
  - Water in **heater-cooler devices** grew *M chimaera*
    - LivaNova (formerly Sorin) Stockert 3T
  - Air samples 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?

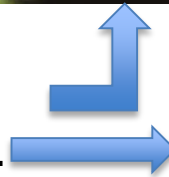


Although water from heater-cooler never contacts patients directly, the circuit is not airtight (or watertight), so the ventilation fan can aerosolize contaminated water from the circuit

# Peeking under the hood...



Chand et al. Clin Infect Dis 2017;64:335-42.  
Lyman, et al. Emerg Infect Dis 2017;23:796.







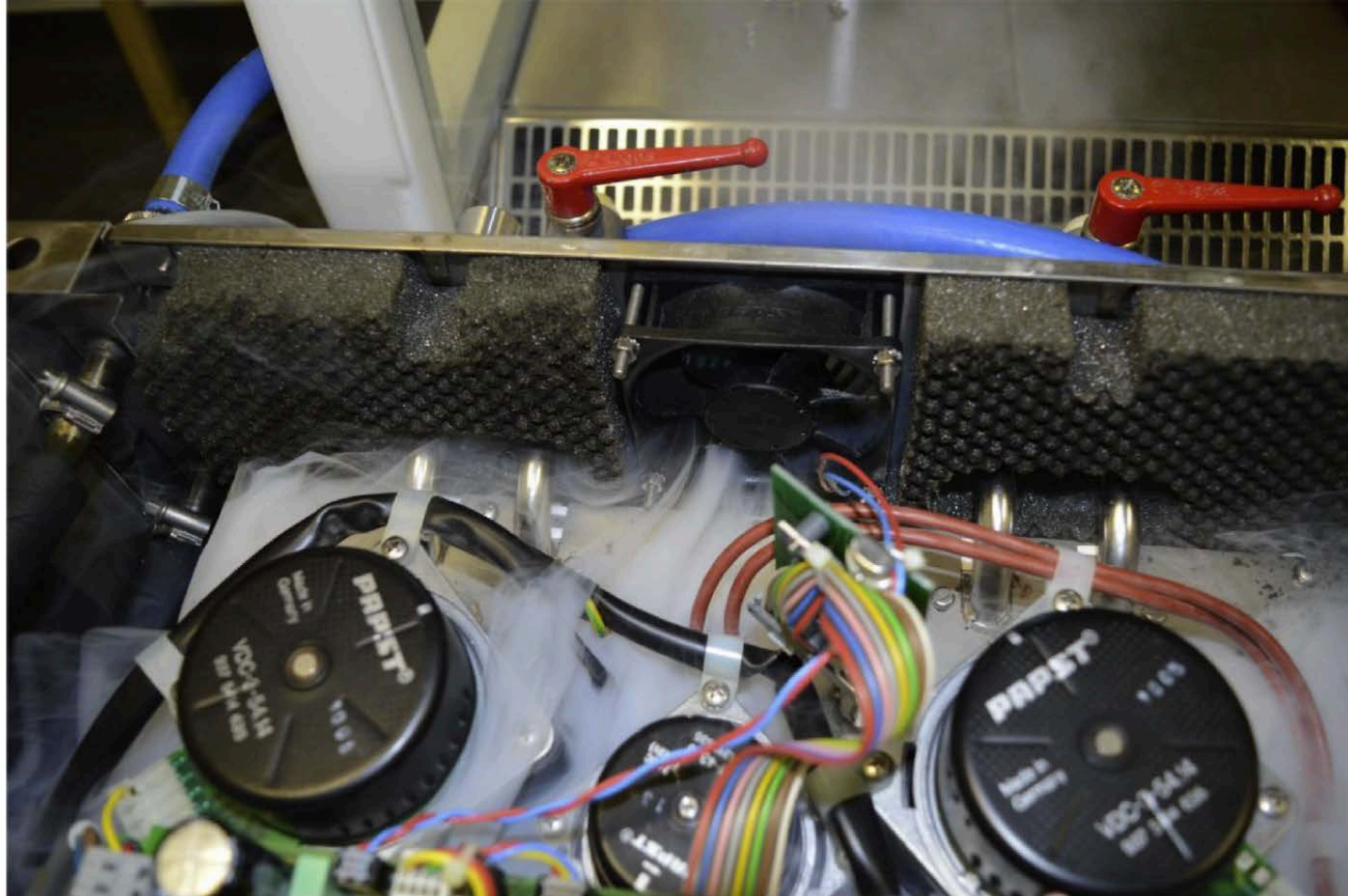
Blocked end of dead-leg pipe

Dead-leg pipe

Debris, biofilm and stagnant water

Overflow pipe

Heater cooler (rear view)



**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.

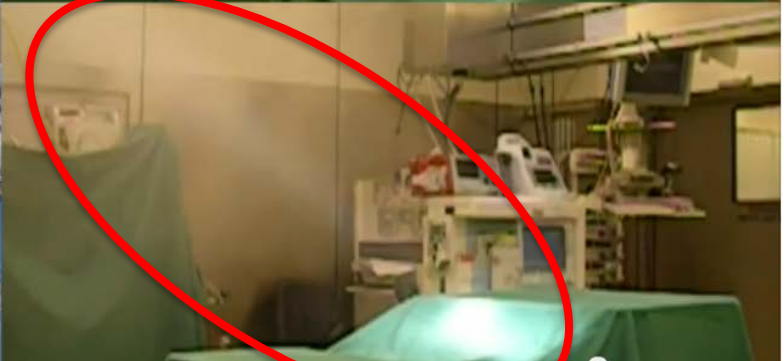
Walker, et al. J Hosp Infect 2017;96:209-220.

# 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.

# 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

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

HCU: heater-cooler unit.

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

Haller S et al. Eurosurveillance 2016;21:17.

# 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)
    - Svensson E, et al. Emerg Infect Dis 2017;23:507-509.
    - 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”

# WGS of 250 isolates worldwide

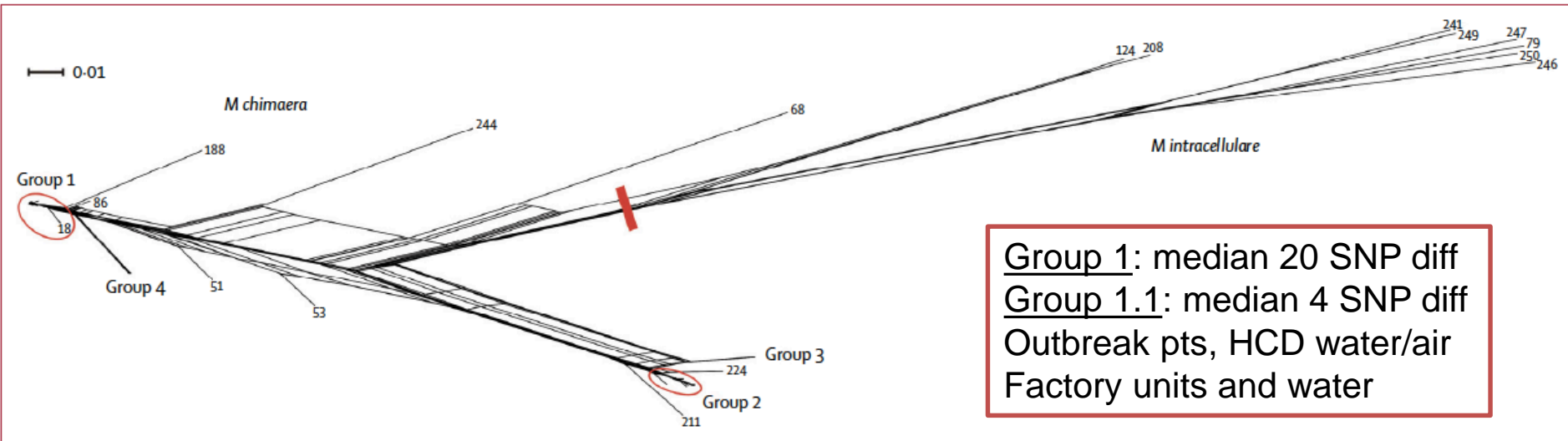


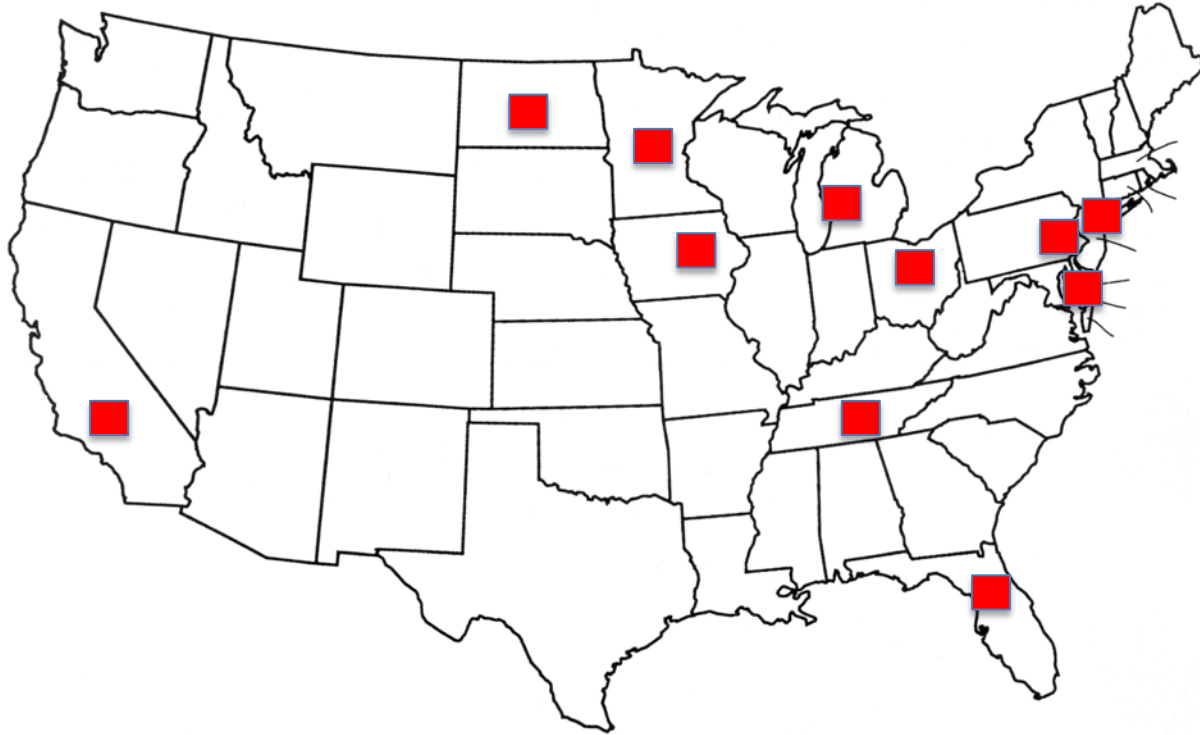
Figure 2: NeighborNet splitstree tree built from 72 545 SNP positions of 250 isolates mapped to the genome of *Mycobacterium chimaera* DSM 44623

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

– van Ingen, et al. Lancet Infect Dis 2017 July 12 (ePub)



# 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/cm<sup>2</sup> 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



# 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)

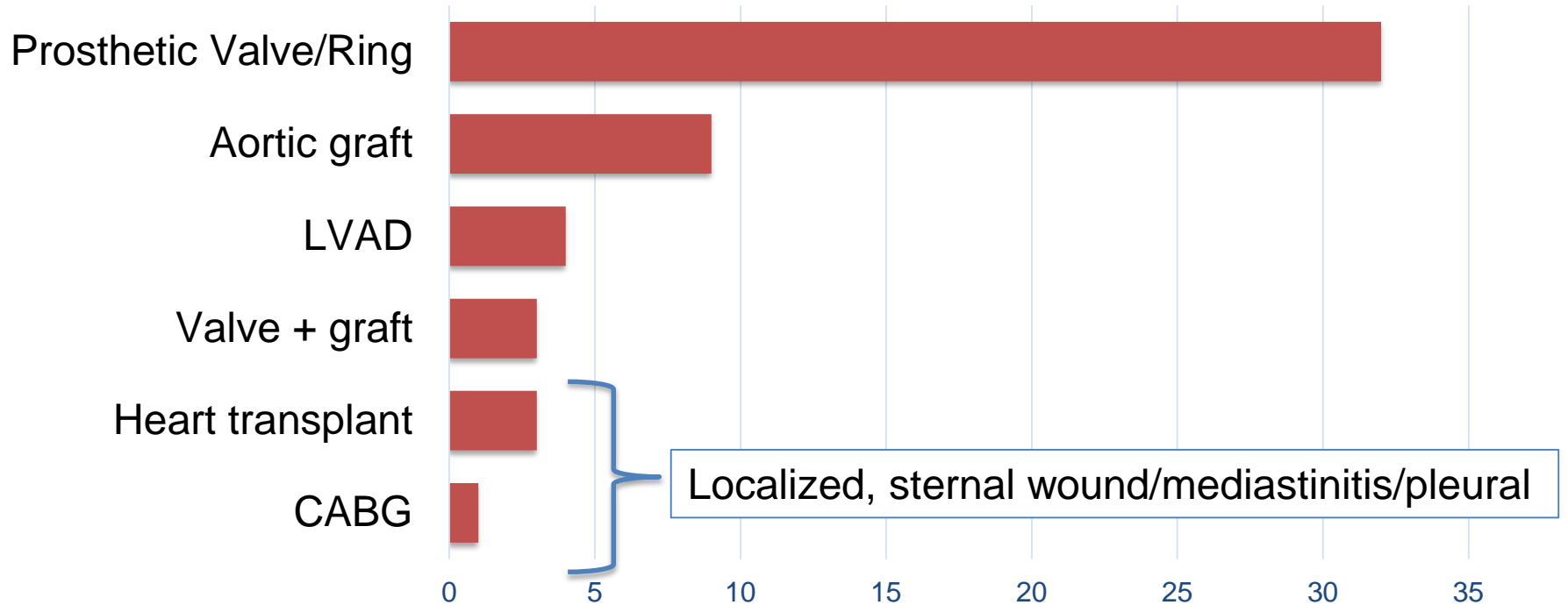
Patient Characteristics	Results
Total number of cases	52
Earliest sentinel surgery	2008
Male	83%
Age, y (mean, range)	60 (1-83)
Prosthetic cardiovascular material	90%
Duration from surgery to symptom onset in months, mean (range)	17 (1-72)
Crude mortality at time of publication or presentation of cases	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 ( $\geq 2$  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.

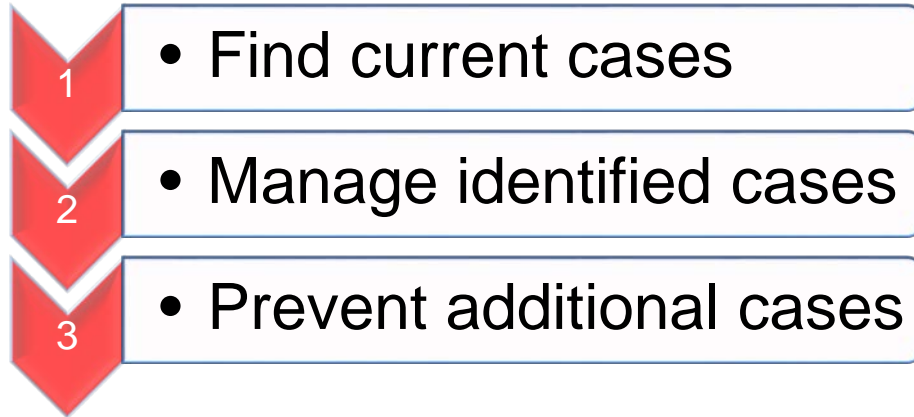
Chand M, et al. Clin Infect Dis 2017;64:335-42.

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

# 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:



# 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>

# 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



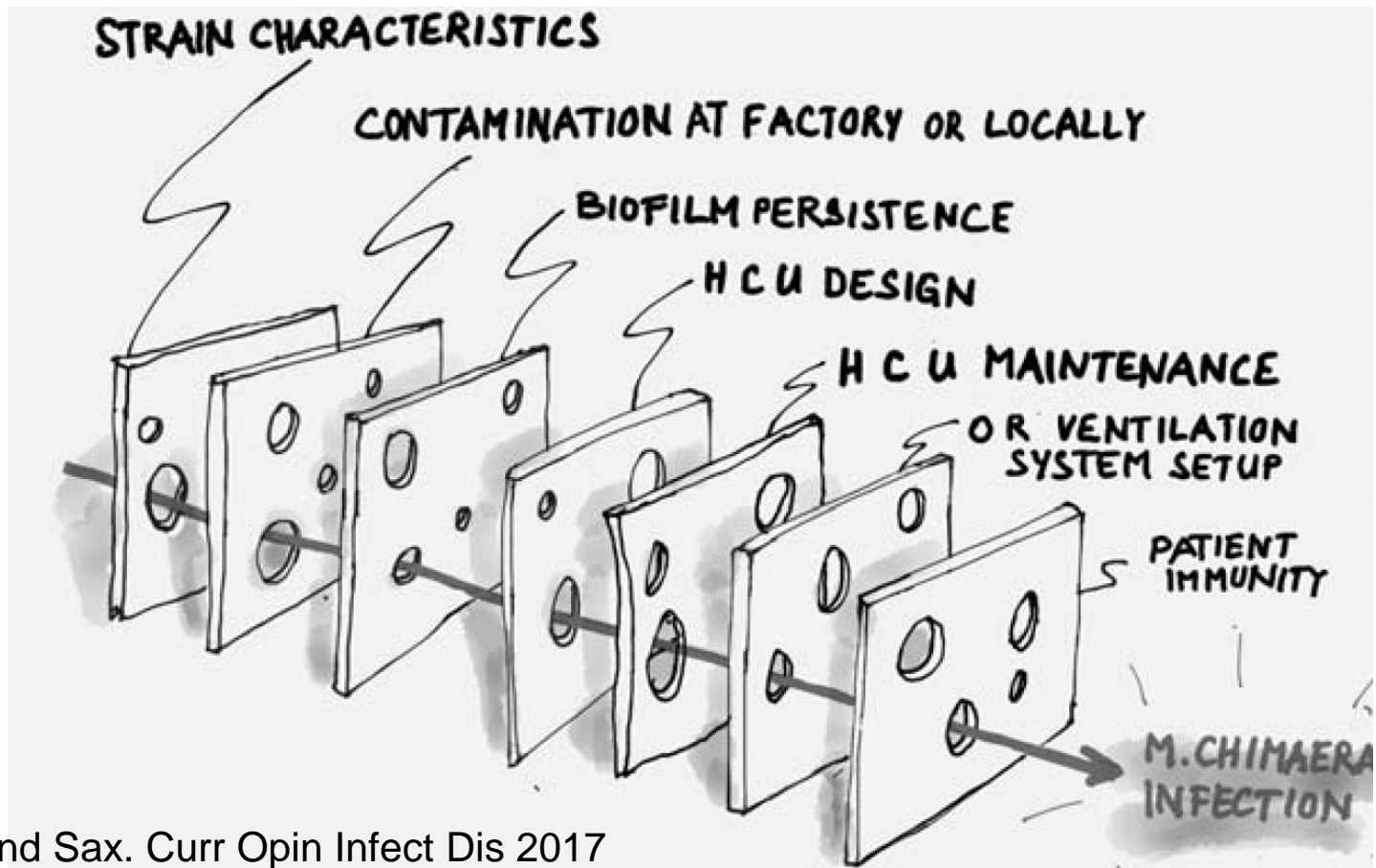
# Case finding: Challenges

- 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

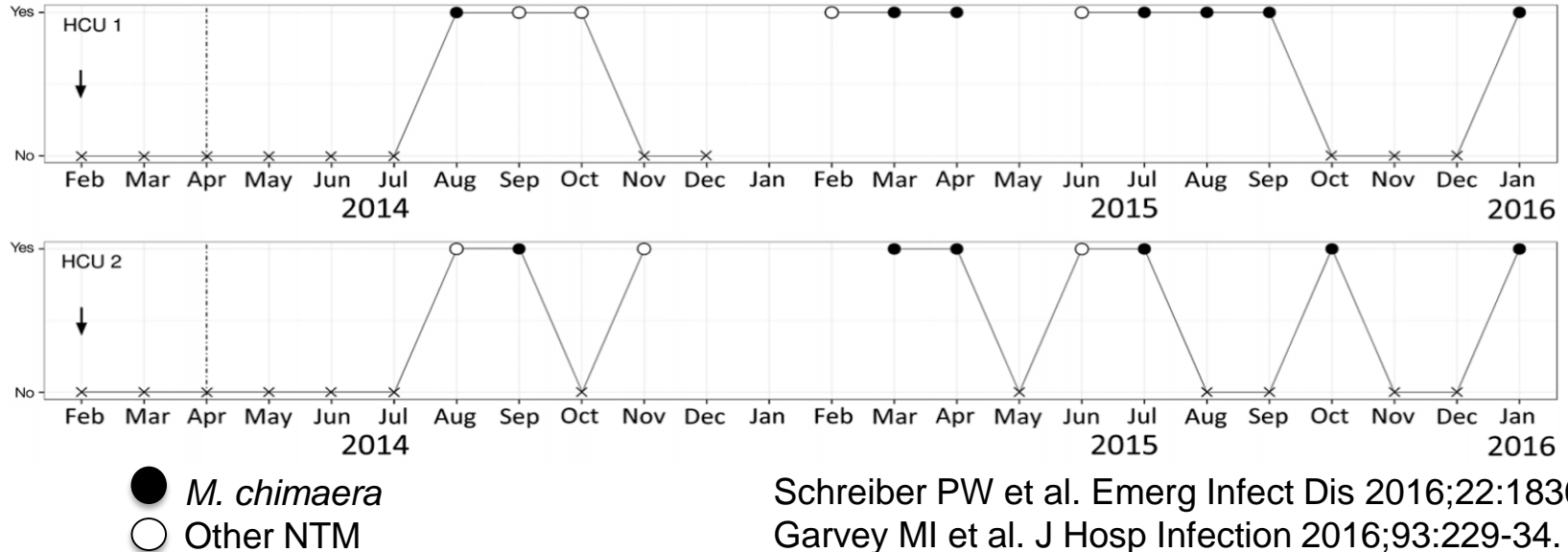


# Prevention measures: HCD management

- 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

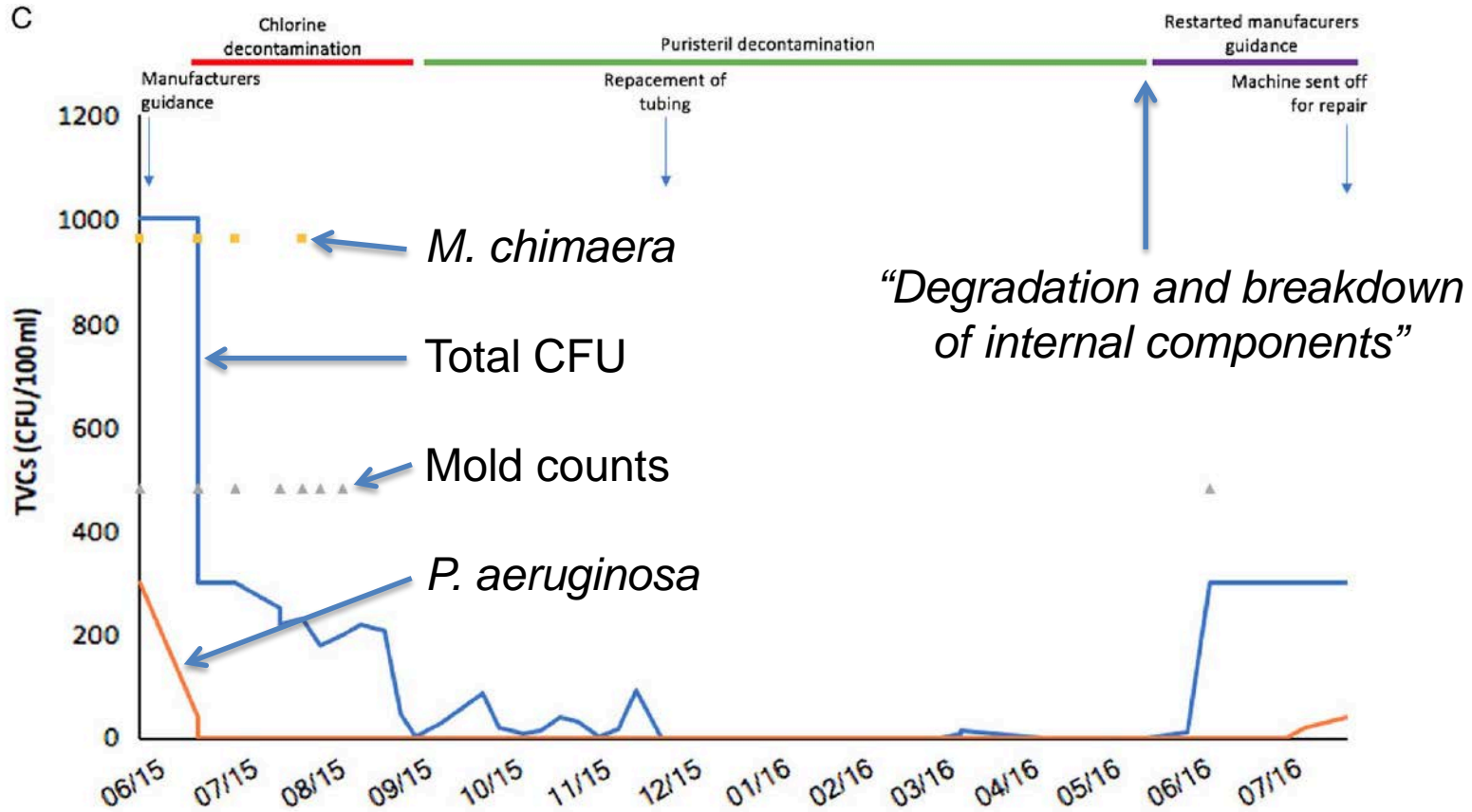
# Can *M. chimaera* be eradicated from HCDs?

- 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<sub>2</sub>O<sub>2</sub>
  - Biweekly disinfection with bleach or peracetic acid + H<sub>2</sub>O<sub>2</sub>



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.

# A year in the life of a contaminated HCU...



# 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 April 19 (ePub).

# Prevention measures:

## Separation of HCD exhaust from OR air

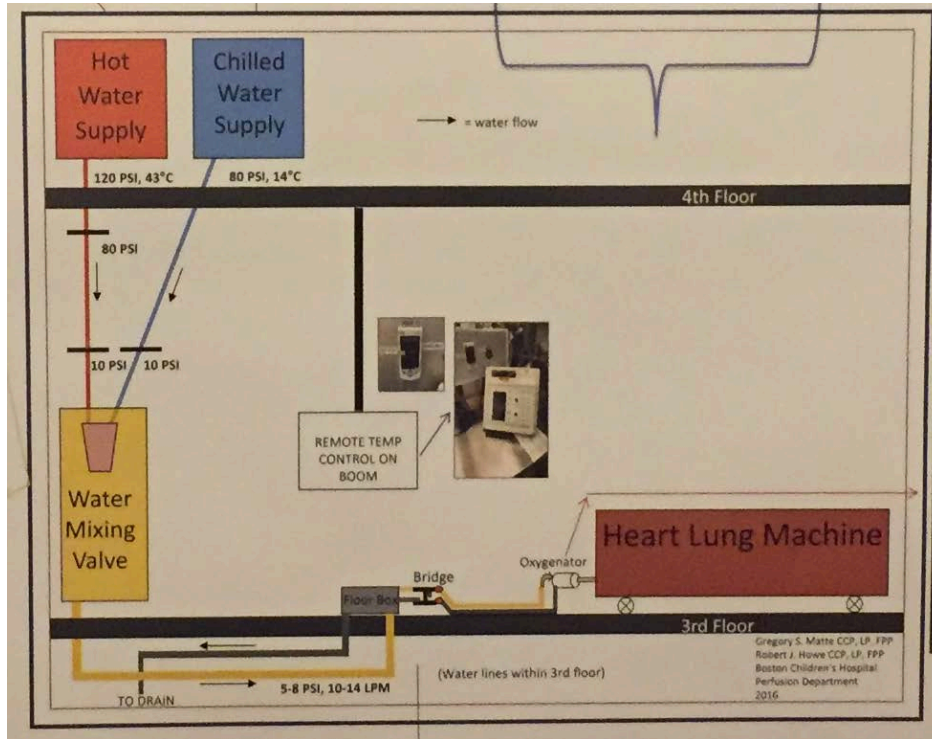


Walker, et al. J Hosp Infect 2017;96:209-220.



# 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.


# LivaNova Implements 3T Heater-Cooler Device Modification

Businesswire

© Aug. 7, 2017, 02:30 AM

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.

Internal sealing  
Vacuum system



# 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 ( $\geq 50\%$ )

# 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 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