Extrapulmonary NTM Infections

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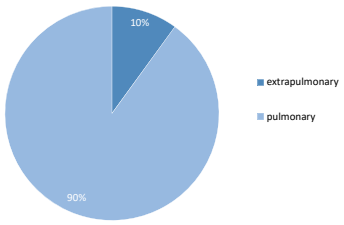
Disclosure

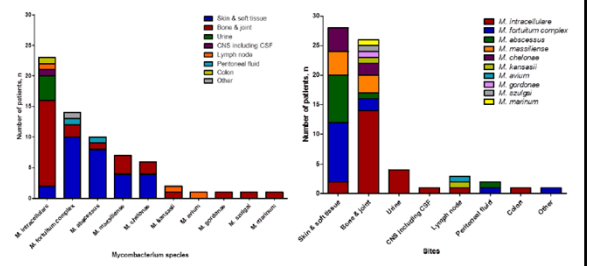
- Nothing to disclose

Objectives

- Introduce the species commonly identified in extrapulmonary infections
- Illustrate several different clinical manifestations
- Review risk factors for extrapulmonary infection
- Discuss the medical and surgical approach in patients with extrapulmonary disease

Clinical Manifestations of NTM





Pathogens 2020;9(11):949

Criteria for NTM disease

- Extrapulmonary
  - Isolation of NTM from a sterile site
  - Concomitant signs of inflammation
    - Preferable to send tissue biopsy or fluid aspirate
    - Wound swab= low yield
    - Send for acid fast smear and culture

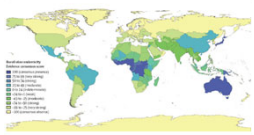
Lymphadenitis

[1]*Tuber Lung Dis* 1995;76:300–310
[2]Pediatr Infect Dis J. 2008;27(10):920

- Sub-acute/chronic unilateral cervical nontender lymphadenitis in children (< 5 years old)
- *M. avium* complex, *M. scrofulaceum, M. malmoense, M. haemophilum*
- ~300 cases/year in US
- Risk factors
  - Children
  - Immunocompromised
  - Protective effect of BCG vaccination?[1]
- Diagnosis: LN biopsy
- Treatment:
  - surgical excision (95% cure)
  - Observation[2]

Buruli Ulcer

- Caused by M. ulcerans (neglected tropical disease)
- Exotoxin (mycolactone)
- Environments with stagnant water?
- Tx: rifampin + streptomycin → all oral regimen; wound management, surgery?



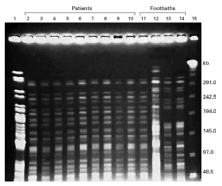
Curr Trop Med Rep 2018;5(4):247-256

Lancet Glob Health 2019;7(7):e912-e922

Nail salon outbreaks

NEJM 2002;346:1366-71

Nail salon outbreaks



Shaving the legs with a razor before pedicure was a risk factor for infection (70 percent of patients vs. 31 percent of controls)

Nail Salon Outbreaks:*M. fortuitum*

- Surgical resection is NOT necessary
- Early antibiotics benefit patients with more than one furuncle
- Untreated skin infection may be self limited
- Mean duration 4 months
- Recommend: quinolone + tetracycline

CID 2004;38(1):38-44.

Fish Tank Granuloma: *M. marinum*

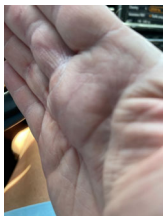
- Solid nodule, plaque or ulceration
- Culture: 33 degrees Celsius
- Risk factors:
  - Contact with aquatic environment (fresh or saltwater)
- Diagnosis: Biopsy with AFB smear and culture

Fish Tank Granuloma: *M. marinum*

- Treatment: 3-4 months with two active agents
  - Clarithromycin/ azithromycin
  - Ethambutol
  - Rifampin
  - Trimethoprim-sulfamethoxazole
  - Doxycycline/minocycline
- Surgery:
  - tendonitis/arthritis
  - failure to respond to standard therapy
- Heat

Dermatology Online Journal 10 (3): 21.

M. Marinum tenosynovitis



- Multiple surgeries
- Azithromycin, ethambutol, rifampin
- Clofazimine
- IV amikacin (limited by tinnitus)
- Drug levels (history of gastric bypass)

Skin, Soft Tissue and Bone Infection

- Nodular skin lesions or ulceration
- Consequence of dissemination or direct inoculation
- Typical pathogens:
  - *Slow growing (M. ulcerans, M. marinum, M. haemophilum, M. avium* complex)
  - Rapidly growing (M. abscessus, M. chelonae, M. fortuitum)
  - Incidence: unknown
- Diagnosis: recommend surgical biopsy of the skin, soft tissue or bone for afb smear and culture

Skin, Soft Tissue and Bone Infection

- Treatment: 2-3 active drugs or more
  - 4 months (or longer) for soft tissue infection
  - 6 months (or longer) for bone infection
  - Erm gene status (inducible macrolide resistance?) for RGM
  - Treat until no clinical or radiological (+/- microbiological) evidence of infection and consider further therapy
- Surgical considerations
  - **Surgical debridement often required - especially in *M. abscessus*, infections of closed space (tendon, joint); removal of foreign material**
  - **Best chance of cure with first debridement, inadequate debridement prolongs antibiotic therapy**
  - Obtain cultures with every surgical intervention

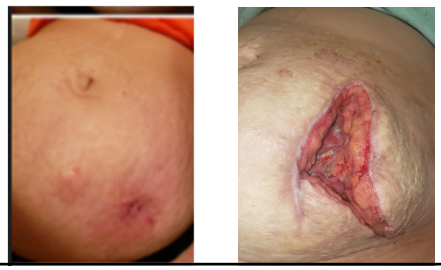
M. Abscessus subsp. abscessus hand infection


Autoimmune hemolytic anemia (prednisone), hearing loss
Tx: IV imipenem + ceftazidime, clofazimine, omadacycline

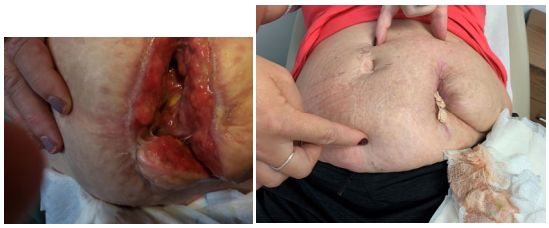

M. Abscessus subsp. abscessus ankle infection

amik/imi/clofaz/linez → imi/ceftaz/clofaz/linez/omada

M. Senegalense abdominal infection



Amikacin, imipenem, clarithromycin, doxycycline, trimethoprim/sulfamethoxazole



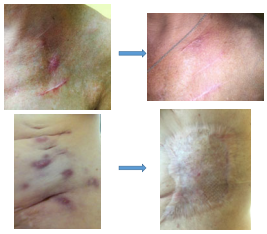
Skin and soft tissue infection (RGM)

Age/sex	Comorbidity	Location	Cause	Organism	Surgery	Antibiotics (weeks)	Outcome (months p Rx)
71 M	DM, CKD	Left palm	trauma	*M. fortuitum*	I/D	AMK,CLR,CIP (4) CLR,CIP (20)	Cure (4)
68 F	Vasculitis	RLE	Public bath	*M. fortuitum, ulcerans and marinum*	None	AMK,CFX,RIF,CLR(3) CLR/MOX (13)	Cure (2)
72 M	COPD*	R shoulder	Post-op 4wks	*M. fortuitum*	I/D	AMK,CFX,CLR (4) DOX,MOX (24)	Cure (3)
71 F	None*	R shoulder	Post-op 6 wks	*M. fortuitum*	I/D	AMK,CFX,CLR (4) CLR,MOX (20)	Cure (4)
78 F	DM,CKD, AI	Left foot	Public bath	*M. chelonae*	Amputa-tion	AMK,CFX,CLR (2) RFT,CLR (6) CLR (3)	Death

* Hardware in place for rotator cuff repair
AMK, amikacin; CFX, cefoxitin; CLR, clarithromycin; CIP, ciprofloxacin; MOX, moxifloxacin;RFT,rifabutin; DOX, doxycycline

Infect Chemother 2013;45(1):85-93.

M. abscessus Post Fat transfer



Abscesses due to *Mycobacterium abscessus* Linked to Injection of Unapproved Alternative Medication

Karin Galil,* Lisa A. Miller,† Mitchell A. Yakrus,* Richard J. Wallace Jr.,‡ David G. Mosley,‡ Bob England,§ Gwen Huitt,¶ Michael M. McNeil,* and Bradley A. Perkins*
*Centers for Disease Control and Prevention, Atlanta, Georgia, USA; †Colorado Department of Public Health and Environment, Denver, Colorado, USA; ‡University of Texas Health Center, Tyler, Texas, USA; §Arizona Department of Health Services, Phoenix, Arizona, USA; and ¶National Jewish Medical and Research Center, Denver, Colorado, USA

An unlicensed injectable medicine sold as adrenal cortex extract (ACE®) and distributed in the alternative medicine community led to the largest outbreak of *Mycobacterium abscessus* infections reported in the United States. Records from the implicated distributor from January 1, 1995, to August 18, 1996, were used to identify

CDC Centers for Disease Control and Prevention — Search

EMERGING INFECTIOUS DISEASES®

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Synopsis

Multistate US Outbreak of Rapidly Growing Mycobacterial Infections Associated with Medical Tourism to the Dominican Republic, 2013–2014[1]

David Schnabel, Douglas H. Esposito, Joanna Gaines, Alison Ridpath, M. Anita Barry, Katherine A. Feldman, Jocelyn Mullins, Rachel Burns, Nina Ahmad, Edith N. Nyangoma, Duc T. Nguyen, Joseph F. Perz, Heather Moulton-Meissner, Bette J. Jensen, Ying Lin, Leah Posivak-Khouly, Nisha Jani, Oliver Morgan, Gary W. Brunette, P. Scott Pritchard, Adena H. Greenbaum, Susan M. Rhee, David Blythe, Mark Sotir, and the RGM Outbreak Investigation Team

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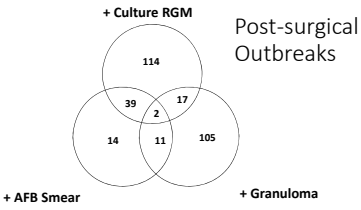
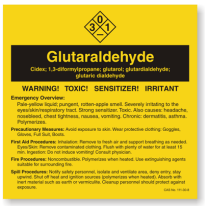


Post-surgical Outbreaks

J Clin Micro 2009;47(7): 2149–2155



- *M. massiliense* BRA100 strain
  - resistant to high gluteraldehyde concentrations (up to 7%)
  - substituted with orthophthaldehyde (OPA) and peracetic acid (PA)-based solutions for high level disinfection

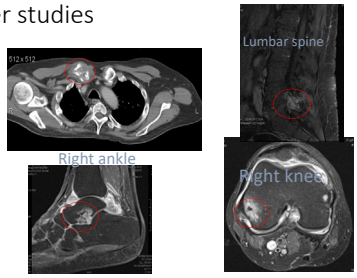
J Clin Micro 2009;47(7): 2149–2155

55 year old male: Arthritis History

Date	Joint	Symptoms	Tap	Rx
2/06	Left knee	Pain/swelling	3000 wbc CPPD crystals	Intrarticular depomedrol
6/06	Left knee	Pain/swelling	CPPD crystals	Intrarticular depomedrol
4/08	polyarthralgias	Pain/swelling	-	-
6/08	Left ankle	Pain/swelling	200 wbc No crystals	Intrarticular depomedrol
6/08-9/08	Left knee/B ankles	Pain/swelling		Intra-articular depomedrol

Left ankle pseudogout?

Further studies



NTM Prosthetic Joint infection(CO)

Location	Knee (4), Hip (2)
Interval from implantation to symptoms	Median 6 months (0-300 mo)
Interval from symptoms to explantation	Median 8.5 months (3-16 mo)
Cure	All (but 1 required hemipelvectomy)

Emerg Infect Dis. 2019 Jun;25(6):1075-1083

NTM Prosthetic Joint infection(CO)

Age	Location	Organism	# of abx	Therapy Duration (mo)	Time to re-implantation (mo)	Cure
48 F	Left Hip	*M. abscessus*	4 (IV)	20	N/A	yes
69F	Right Hip	*M. fortuitum*	4 (IV)	5	4	yes
79M	Left knee	MAC	4 (IV)	39	12	yes
77F	Right knee	MAC	3	9	7	yes
83M	Left knee	*MAC*	3	7	5	yes
49F	Right knee	*M. gordonae*	4 (IV)	16	6	yes

2009-2015

Emerg Infect Dis. 2019 Jun;25(6):1075-1083

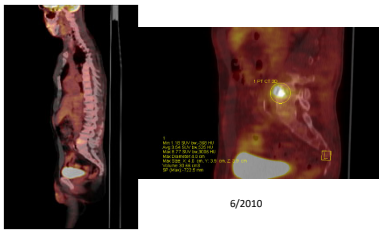
Prosthetic Joint infection

- Most patients >60 years old & immunocompetent
- Culture yield
  - Mycobacterial culture (100%)
  - NTM recovered in routine culture low (1/9)
- Only patients with resection arthroplasty (REA) attained cure
- Duration of effective antibiotic therapy
  - post REA 16-55 weeks
- Staged re-implantation:
  - successful in 3/6 without lifelong suppressive antibiotics
  - 30+ weeks after REA
- Retention of prosthesis (4), all *M. fortuitum*
  - Successful in 2/4 with suppressive antibiotics

CID 2007;45:687-94.

50 year old Male

50 year old Male



6/2010

MAC Vertebral Osteomyelitis

- 9th year of infection
- 3 Debridements
- 10/08 Anterior fusion with cadaveric graft (failed)
- 10/13 Posterior T11-Sacral fusion
- Still with persistent anterior hardware
- Chronic Azithromycin + clofazimine

Vertebral osteomyelitis

- Series 38 cases 1965-2003
  - *M. avium* complex (22), *M. xenopi* (3), *M. fortuitum* (6), *M. abscessus* (3) *M. bovis* (1) *M. simiae* (1), *M. celatum* (1).
  - Mean age 56
  - ~30% immunosuppressed
  - Most frequent sites: lower thoracic, upper lumbar
  - Trauma (4)
  - Post-laminectomy (1)

J Infect Chemother. 2013 Oct;19(5):972-7.

Vertebral osteomyelitis

- Treatment: no consensus
  - surgical and antimicrobial therapy is often required to completely eradicate the infection.
  - Indications for early surgery: progressive destruction of vertebral bodies, neurological compression, and abscess formation, drug resistant organism

Catheter related blood stream infections

*N=11 CRBSI w/ RGM
- Oncology patients
- 6/11 neutropenic
- 4/4 cured w removal + antibiotics
- 7/7 failure with antibiotics alone

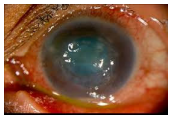
No official recommendations exist for the choice of antibiotics or duration

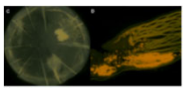
Suggest: 2 active antibiotics for a minimum of 2 months with resolution of symptoms and removal of the line

MUST REMOVE

Diagn Microbiol Infect Dis. 2008 Jun;61(2):187-91.
Pediatr Infect Dis J. 2003 Dec;22(12):1108-9.
*Rev Infect Dis. 1991 Nov-Dec;13(6):1120-5.

NTM Keratitis

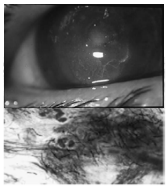




- Inflammation of the cornea
- Indolent (>3.5 wk) pain redness, photophobia, decreased vision
- Most common NTM: RGM (M. *chelonae)*
- Risk Factors:
  - LASIK,
  - eye surgery
  - contact lens use
- Dx: early irrigation/culture

NTM Keratitis

- Triple Topical Treatment: amikacin, clarithromycin + moxifloxacin gtts +/- PO macrolide
- Rx: No consensus on duration
- Surgery: indications for flap removal
  - Nonadherence of the flap
  - Lack of clinical improvement on medical therapy
- Avoid topical corticosteroids



Int Ophthalmol Clin. 2007;47(2):73-84.
J Cataract Refract Surg 2010; 36:843–846

Disseminated Disease

- Typical presentation : HIV/AIDS
  - (CD4 <50)
- Any of the NTM can cause dissemination
  - >90% secondary to *M. avium* complex
- Introduced: lungs or intestinal tract
- Clinical presentation
  - Fever, night sweats, weight loss, diarrhea
  - Bacteremia (intermittent), elevated alkaline phosphatase, LDH, anemia

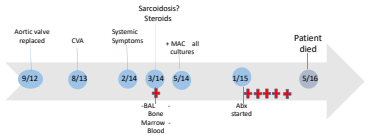
Disseminated Disease

- Incidence
  - DMAC ~40% of AIDS patients with CD4 of <10
  - 3.7/100 person years → 0.9/ 100 person years in the HAART era
- Risk factors: Immunocompromised, central line infection
- Diagnosis: + blood cultures
  - Recommend liquid and solid medium
  - 96% + in liquid culture by 14 days
- Treatment:
  - Clarithromycin/azithromycin + ethambutol +/- rifabutin
  - Key to success in HIV/AIDS is antiretroviral therapy

- A 53 year old male describes cryptic fevers for 3 months and fatigue. He has a normal exam apart from an well healed sternotomy incision related to AVR 6 years ago. His labs note anemia, hepatitis and an elevated creatinine.
- Blood cultures are + for MAC.
- What is this related to?

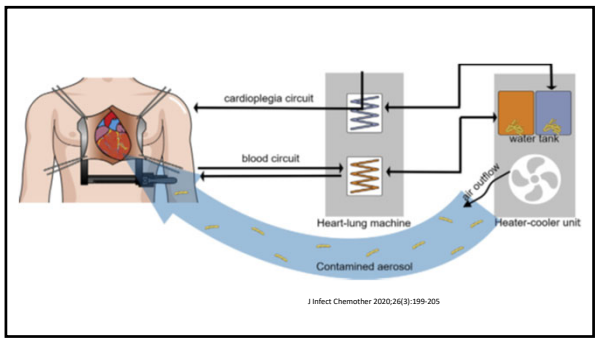
1. HIV infection
2. Idiopathic CD4 lymphopenia
3. Contamination of a device from the OR 6 years ago

Clinical Case

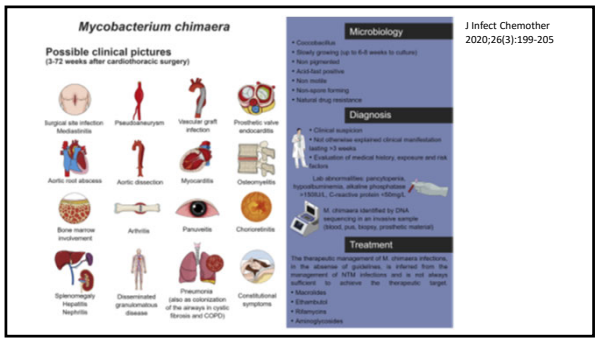


The Outbreak: Heater-Cooler Units

·Warm or cool a patient to an optimal temperature
-250,000 procedures in the US/year
-3T: 60% US market share



J Infect Chemother 2020;26(3):199-205



J Infect Chemother 2020;26(3):199-205

J Infect Chemother 2020;26(3):199-205

Table 1
Case definition of M. chimaera infections potentially associated with heater-cooler units.

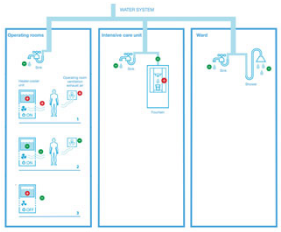
CLINICAL CRITERIA	EXPOSURE CRITERIA
Any of the following: • Prosthetic valve endocarditis • Prosthetic vascular graft infection • Sternotomy wound infection • Mediastinitis • Manifestation of disseminated infection including embolic and immunologic manifestations, e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis, myocarditis.	Surgery requiring cardiopulmonary bypass in the five years prior to the onset of symptoms of infection.
CONFIRMED CASE Clinical + exposure criteria + M. chimaera detected and identified by DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)	
PROBABLE CASE • Clinical + exposure criteria + M. chimaera detected by direct PCR and amplified DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material) • Clinical + exposure criteria + MAC detected by culture or direct PCR from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material) • Clinical + exposure criteria + histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid-fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound.	

MAC = Mycobacterium avium complex.
PCR = Polymerase chain reaction.
Adapted from 2015 ECDC case definition [22].

Prolonged outbreak of *M. chimaera* infection after open-chest heart surgery

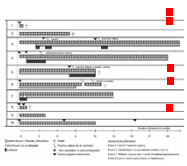
- N= 6 males affected between 2006-2012
- Ages 49-64
- Sx: fatigue, fever, hepatitis, splenomegaly, renal insufficiency, pancytopenia
- Latency of symptoms : 1.5-3.6 years
- 5/6 abnormal echocardiogram
- 3/6 underwent PV replacement
- 1 repeated surgical debridement
- 2/6 died despite antibiotic therapy

Sax, H et al. Clinical Infectious Diseases 2015;61(1)67-75.



Sax,H et al. Clinical Infectious Diseases 2015;61(1)67-75.

Healthcare associated *M. chimaera* infections subsequent to open heart surgery



- 10 patients with disseminated *M. chimaera*
- 3 European hospitals
- Latency 18 months (median)
- Diagnosis 21 months (median)
- Fever, SOB, fatigue, wt loss
- Splenomegaly
- Anemia, lymphocytopenia, thrombocytopenia
- Rx: macrolide/rifamycin/ethambutol
- +/- amikacin, quinolone
- 8/10 treatment failure, 5 deaths

Kohler P, et al. Eur Heart J 2015;36:2745-53.

> J Infect. 2020 Feb;80(2):197-203. doi: 10.1016/j.jinf.2019.12.007. Epub 2019 Dec 19.

Long-term follow-up of post-cardiac surgery Mycobacterium chimaera infections: A 5-center case series

Kathleen G Julian [1], Tonya Crook [2], Eugene Curley [3], A Ben Appenheimer [4], Catharine I Paules [1], Barbara Hasse [5], Daniel J Diekema [4], Charles L Daley [6], Jorgelina de Sanctis [7], Walter C Hellinger [8], Ashah Levin [9], George McCherry [4], Carol Freer [1], Cynthia J Whitener [1]

Affiliations + expand

PMID: 31863789 DOI: 10.1016/j.jinf.2019.12.007

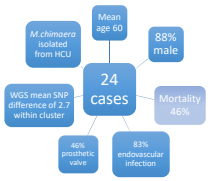
Disseminated *Mycobacterium chimaera* Infection After Cardiothoracic Surgery

Nicholas Tan,[1] Rahul Sampath,[2] Omar M. Abu Saleh,[2] Marysia S. Tweet,[3] Dragan Jevremovic,[4] Saba Alnaemi,[5] Nancy L. Wengenack,[1,4] Priya Sampathkumar,[2] and Andrew D. Badley[2]

[1]Department of Internal Medicine, [2]Division of Infectious Disease, [3]Division of Cardiovascular Diseases, [4]Department of Hematopathology, [5]Department of Ophthalmology, and [6]Division of Clinical Microbiology, Mayo Clinic College of Medicine, Rochester, Minnesota

Tan N et el. Open forum Infect Dis 2016:3:ofw131.

Experience from four US healthcare systems



Appenheimer AB, ID Week 2016 (Abstract 2392)

Clinical Presentation

Time to Presentation – median 21 months (5-40)

Symptoms	Fever, Fatigue, Weight loss, Shortness of breath
Signs	Splenomegaly Chorioretinitis
Laboratory Values	Anemia, Lymphocytopenia, Thrombocytopenia, Elevated CRP Elevated transaminases Elevated creatinine

Achermann Y, et al. J Clin Microbiol 2013;51:1769
Sax H, et al. Clin Infect Dis 2015;61:67
Kohler P, et al. Eur Heart J 2015;36:2745

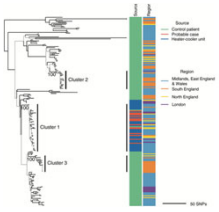
Manifestation of Infections

- Prosthetic valve endocarditis
- Vascular graft infection
- Manifestations of disseminated disease:
  - Emboli
  - Bone marrow involvement
  - Splenomegaly
  - Nephritis
  - Myocarditis
  - Osteomyelitis

Achermann Y, et al. J Clin Microbiol 2013;51:1769
Sax H, et al. Clin Infect Dis 2015;61:67
Kohler P, et al. Eur Heart J 2015;36:2745

M. chimaera typing

Phylogenetic analysis found close clustering of strains from probable cases



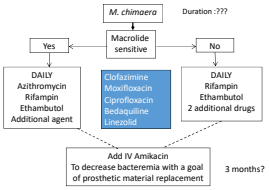
Chand et al. Clinical Infectious Diseases 2017;64 (3)335-42.

The Outbreak Summary

- An outbreak with global distribution
- Worldwide case count >=150 in 2019
- The isolates from Europe, US and Australia are genetically identical
- The source of contamination originated at the manufacturing site

Trans Am Clin Climatol Assoc. 2019;130:136-144.

Treatment Disseminated *M. chimaera*



Clin Infect Dis. 2019 Mar 19;68(7):1244-1250

Move the unit

Courtesy of Jakko van Ingen

Extrapulmonary NTM: Summary

- Sub-acute, chronic
- Consider:
  - immunocompromised patient or post-operative patient with a sub-acute presentation
- Must be have a high index of suspicion
- Avoid monotherapy
- Treatment is measured in months
- Remove all foreign material
- *M. abscessus*
  - Pathogenicity + drug resistance
  - surgical debridement is often necessary for cure

Questions ?