Risk Factors and Outcomes of *Mycobacterium abscessus* Complex Acquisition after Lung Transplantation

Presented by:
Sophie E. Nick, BA
Duke University School of Medicine

Co-authors:
Michael E. Yarrington, MD, MMCi
John M. Reynolds, MD
Deverick J. Anderson, MD, MPH
Arthur W. Baker, MD, MPH

Duke University School of Medicine

dcasip.medicine.duke.edu

Duke Center for Antimicrobial Stewardship and Infection Prevention

Disclosures

- Stead Program of the Duke University Department of Medicine:
  - Sophie Nick
- National Institute of Allergy and Infectious Diseases (NIAID) of NIH:
  - K08-AI163462 (Baker)

All relevant financial disclosures have been mitigated

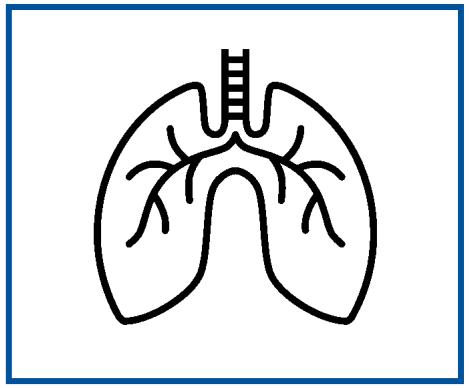
Background: *Mycobacterium abscessus* Complex (MABC)

- Rapidly-growing mycobacterium (RGM)
  - 3 subspecies: *M. abscessus, M. massiliense, M. bolletii*
- One of the most difficult to treat nontuberculous mycobacteria (NTM)

Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Lee MR, et al. *Emerg Infect Dis*. 2015;21(9):1638-1646

Background: *Mycobacterium abscessus* Complex (MABC)

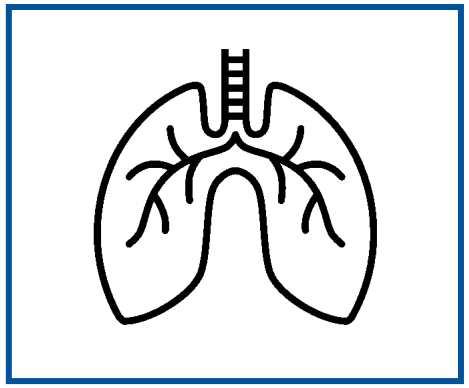
- Rapidly-growing mycobacterium (RGM)
  - 3 subspecies: *M. abscessus, M. massiliense, M. bolletii*
- One of the most difficult to treat nontuberculous mycobacteria (NTM)
- Clinical manifestations:

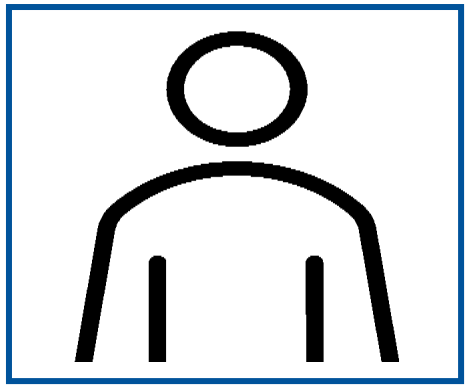


Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Lee MR, et al. *Emerg Infect Dis*. 2015;21(9):1638-1646

Background: *Mycobacterium abscessus* Complex (MABC)

- Rapidly-growing mycobacterium (RGM)
  - 3 subspecies: *M. abscessus, M. massiliense, M. bolletii*
- One of the most difficult to treat nontuberculous mycobacteria (NTM)
- Clinical manifestations:

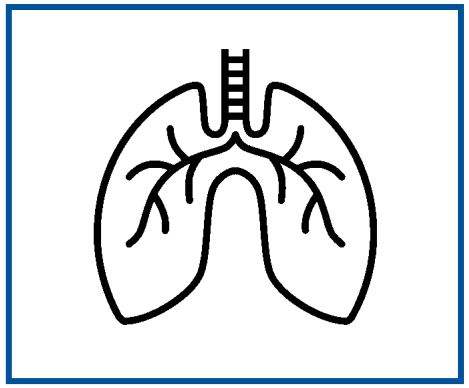


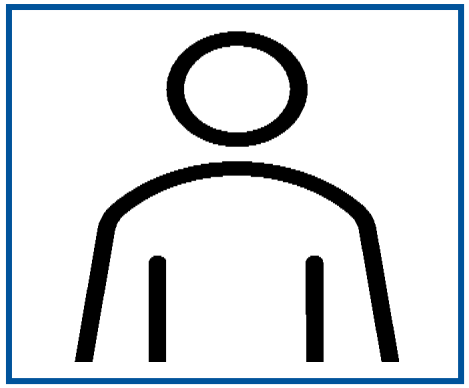


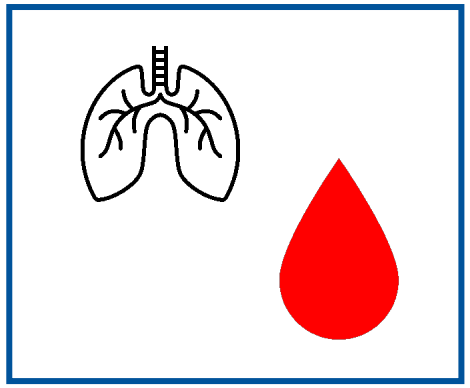
Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Lee MR, et al. *Emerg Infect Dis*. 2015;21(9):1638-1646

Background: *Mycobacterium abscessus* Complex (MABC)

- Rapidly-growing mycobacterium (RGM)
  - 3 subspecies: *M. abscessus, M. massiliense, M. bolletii*
- One of the most difficult to treat nontuberculous mycobacteria (NTM)
- Clinical manifestations:



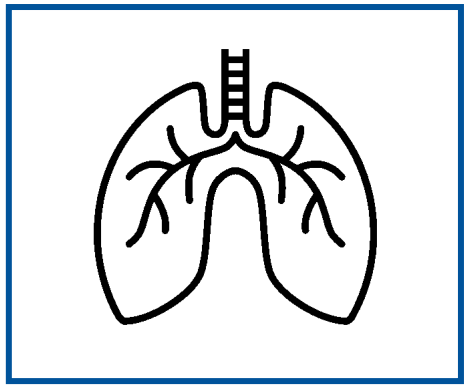
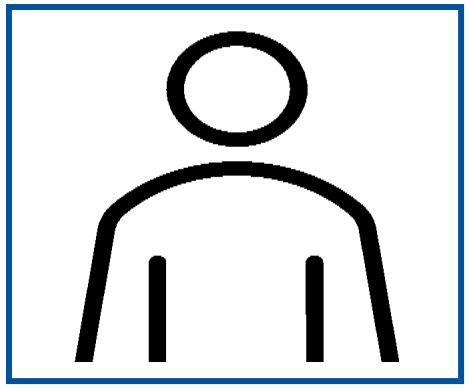
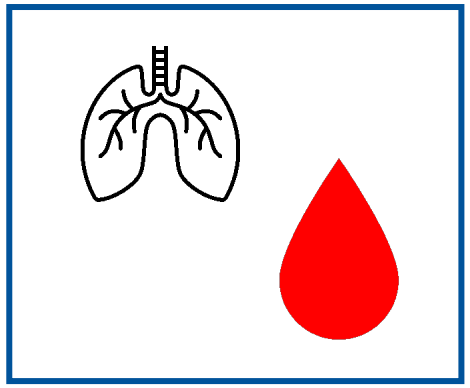
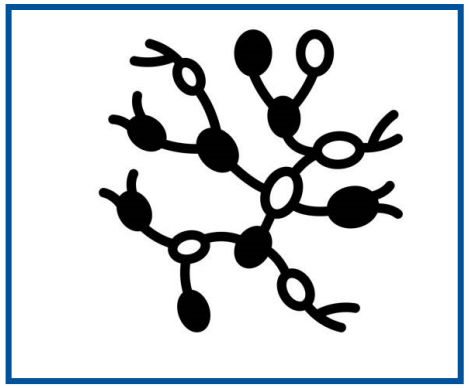




Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Lee MR, et al. *Emerg Infect Dis*. 2015;21(9):1638-1646

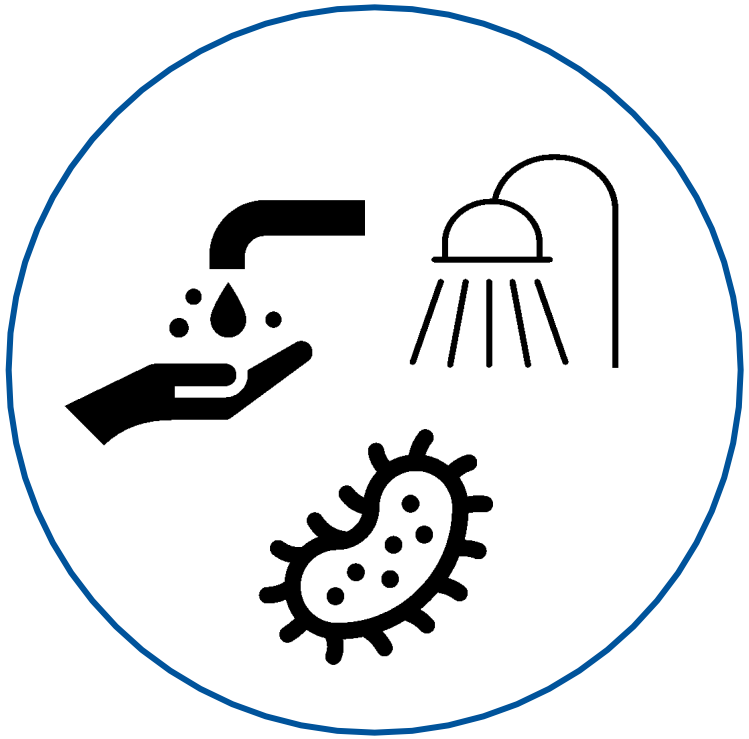
Background: *Mycobacterium abscessus* Complex (MABC)

- Rapidly-growing mycobacterium (RGM)
  - 3 subspecies: *M. abscessus, M. massiliense, M. bolletii*
- One of the most difficult to treat nontuberculous mycobacteria (NTM)
- Clinical manifestations:

Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Lee MR, et al. *Emerg Infect Dis*. 2015;21(9):1638-1646

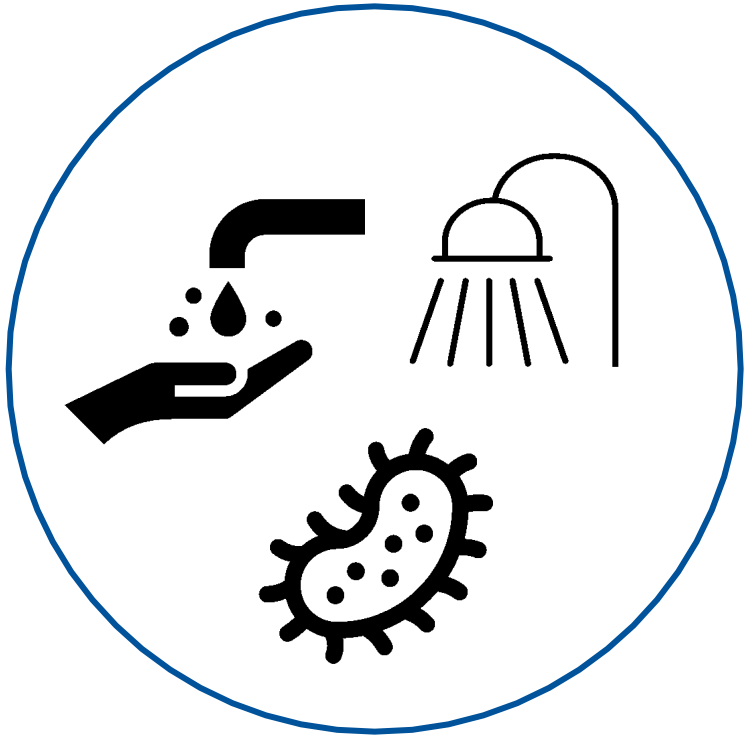
Healthcare Associated Outbreaks



Forms biofilms → Leads to persistence

Baker AW, et al. *Clin Infect Dis.* 2021;73(3):333-339
CDC: Healthcare-Associated Infections – "Reduce Risk from Water." 2019

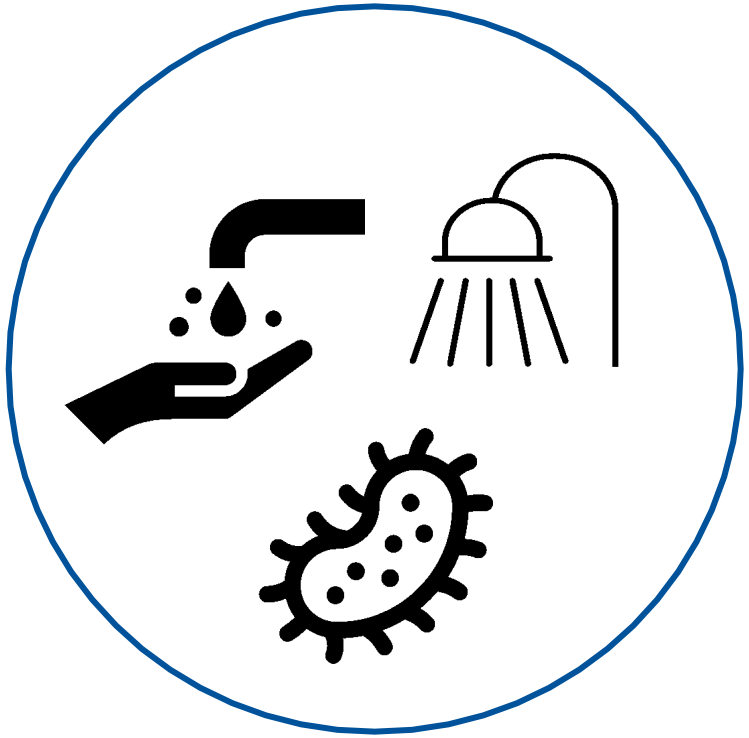
Healthcare Associated Outbreaks

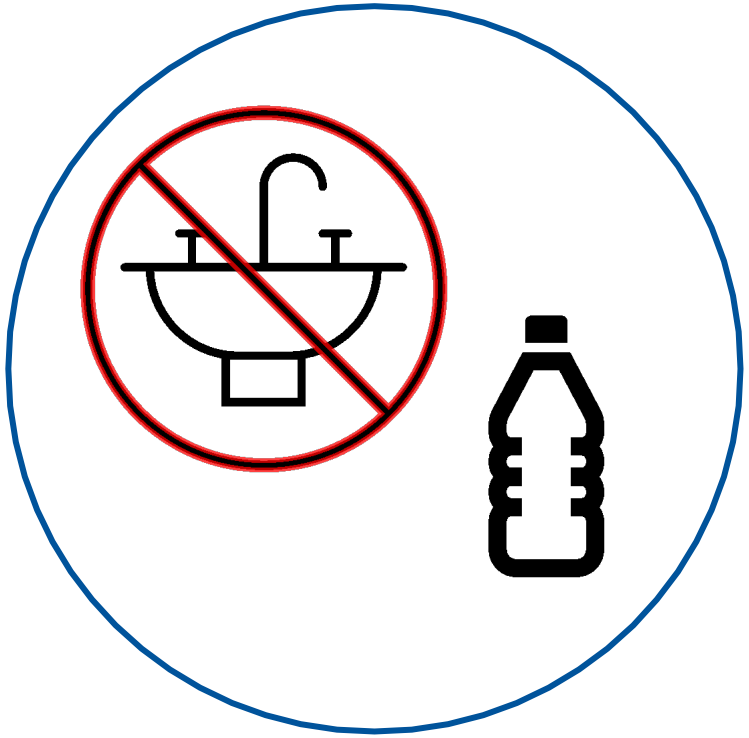


Forms biofilms → Leads to persistence

Baker AW, et al. *Clin Infect Dis.* 2021;73(3):333-339
CDC: Healthcare-Associated Infections – "Reduce Risk from Water." 2019

Healthcare Associated Outbreaks



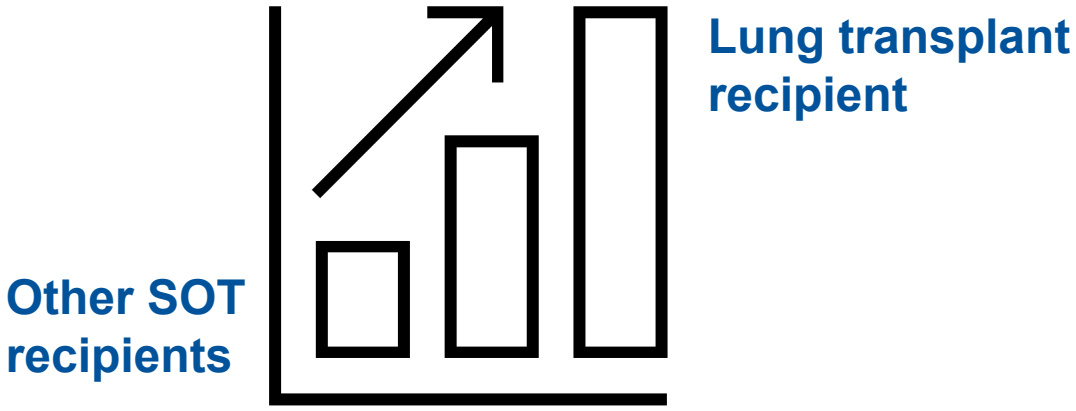


Forms biofilms → Leads to persistence

Baker AW, et al. *Clin Infect Dis.* 2021;73(3):333-339
CDC: Healthcare-Associated Infections – "Reduce Risk from Water." 2019

Risk of Acquisition Post-Transplant

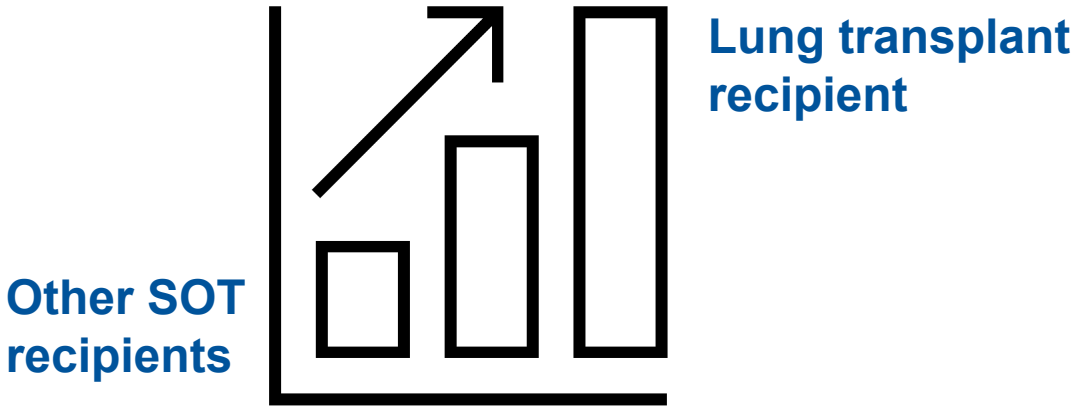
- Known risk factors for NTM pulmonary infection still apply
- Solid organ transplant (SOT) recipients at increased risk



Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Longworth SA, et al. *Transpl Infect Dis*. 2014;16(1):76-83

Risk of Acquisition Post-Transplant

- Known risk factors for NTM pulmonary infection still apply
- Solid organ transplant (SOT) recipients at increased risk



- Few previous studies looked at:
  - Risk factors after lung transplant
  - Specifically examined MABC
  - Extrapulmonary disease
  - Early post-transplant period

Drummond WK, et al. *Thorac Surg Clin*. 2019;29(1):59-64
Longworth SA, et al. *Transpl Infect Dis*. 2014;16(1):76-83

Objective and Methods

- Objective: Determine specific risk factors for M. abscessus acquisition in the first 90 days after transplant

- Methods: Retrospective matched case-control study
  - Patients who underwent lung transplant at Duke between 2012-2021

Methods

- Retrospective matched case-control study

- **Case:** *De novo* MABC acquisition within 90 days post-transplant

- **Control:** No positive MABC cultures

- **Matching:** 1 case to 3 controls
  - Age +/- 5 years
  - Transplant date +/- 1 year

Statistical Analysis

- **Univariate Analysis:** Case and control characteristics and outcomes for 1-year post-transplant were compared using conditional logistic regression

Statistical Analysis

- **Univariate Analysis:** Case and control characteristics and outcomes for 1-year post-transplant were compared using conditional logistic regression
- **Multivariate Reference Model:** Conditional logistic regression model used to determine independent risk factors for MABC acquisition
  - Included variables with P value ≤0.20 (after accounting for collinearity and epidemiologic plausibility)

Statistical Analysis

- **Univariate Analysis:** Case and control characteristics and outcomes for 1-year post-transplant were compared using conditional logistic regression
- **Multivariate Reference Model:** Conditional logistic regression model used to determine independent risk factors for MABC acquisition
  - Included variables with P value ≤0.20 (after accounting for collinearity and epidemiologic plausibility)
- Survival probabilities were calculated using the Kaplan-Meier method

Results: Patient Characteristics

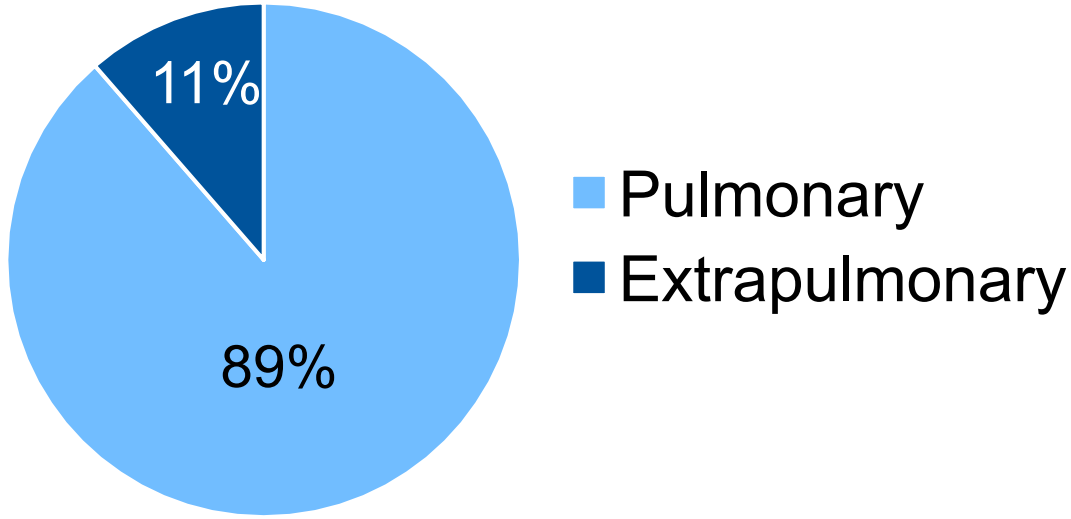
- Total of **1,110 unique patients** underwent lung or heart-lung transplant between 2012 – 2021 at Duke
- **79 (7.1%)** met the case inclusion criteria
  - Matched with 237 controls

Results: Patient Characteristics

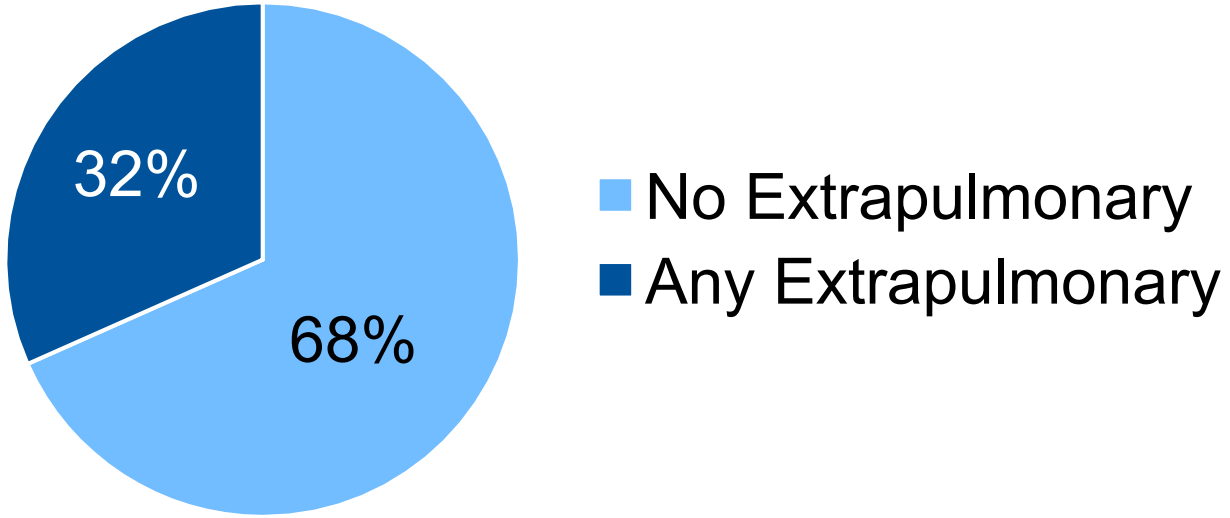
- Total of **1,110 unique patients** underwent lung or heart-lung transplant between 2012 – 2021 at Duke
- **79 (7.1%)** met the case inclusion criteria
  - Matched with 237 controls
- No difference in age, sex, ethnicity, or race between cases and controls
- Median time to isolation post-transplant was **33 days** (IQR 11-59)

MABC Cases

Specimen Site of First Positive Culture

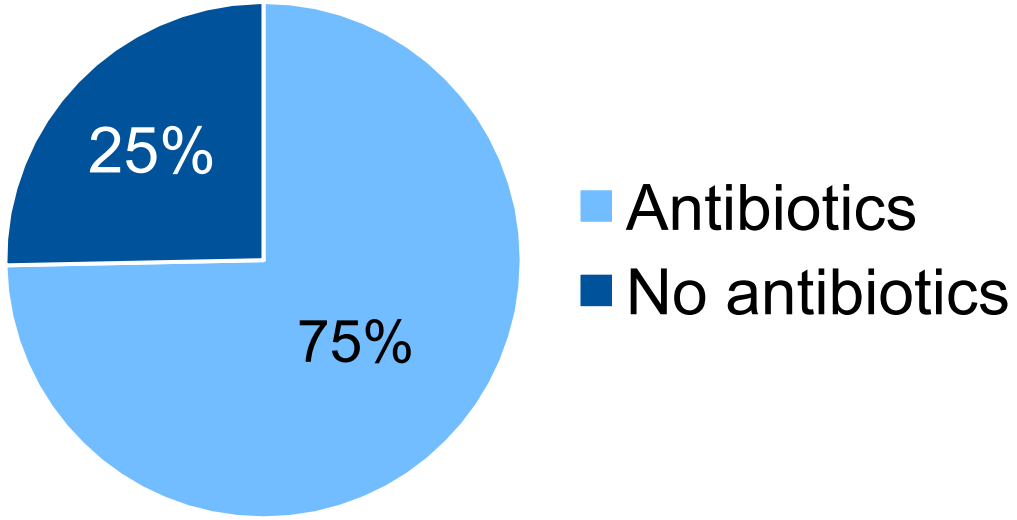


Specimen Site of All Cultures

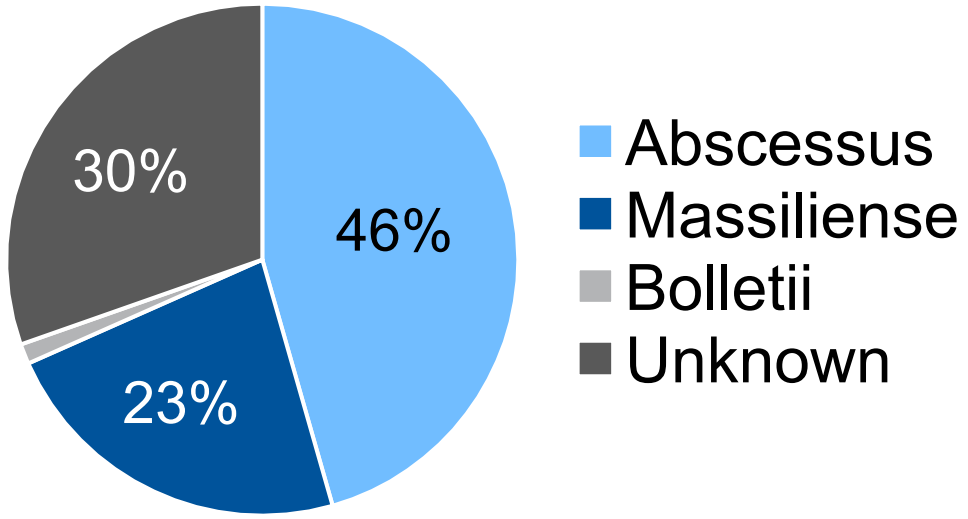


MABC Cases

Received Antibiotics Targeting MABC



Subspecies of Isolates

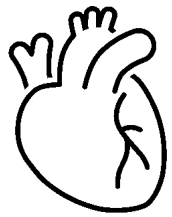


Univariate Analysis: Preoperative Characteristics of Cases vs Controls

Risk Factors

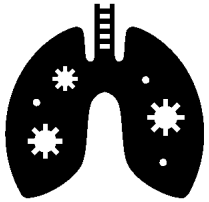
Karnofsky Performance Status Score ≤30% **P = 0.04**

Ventilator immediately prior to transplant **P = 0.02**



ECMO immediately prior to transplant **P = 0.03**

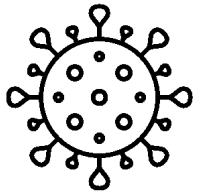
Protective Factors



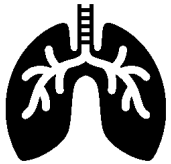
Idiopathic Pulmonary Fibrosis Diagnosis **P = 0.04**

Univariate Analysis: Perioperative Characteristics of Cases vs Controls

Risk Factors

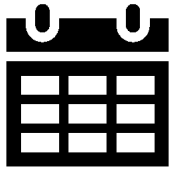


CMV mismatch with their donor (donor + / recipient – serology) **P = 0.05**



Bilateral lung transplant **P = 0.04**

Post-transplant ventilator ≥2 days **P <0.001**



More days in the hospital between transplant and index date **P <0.01**

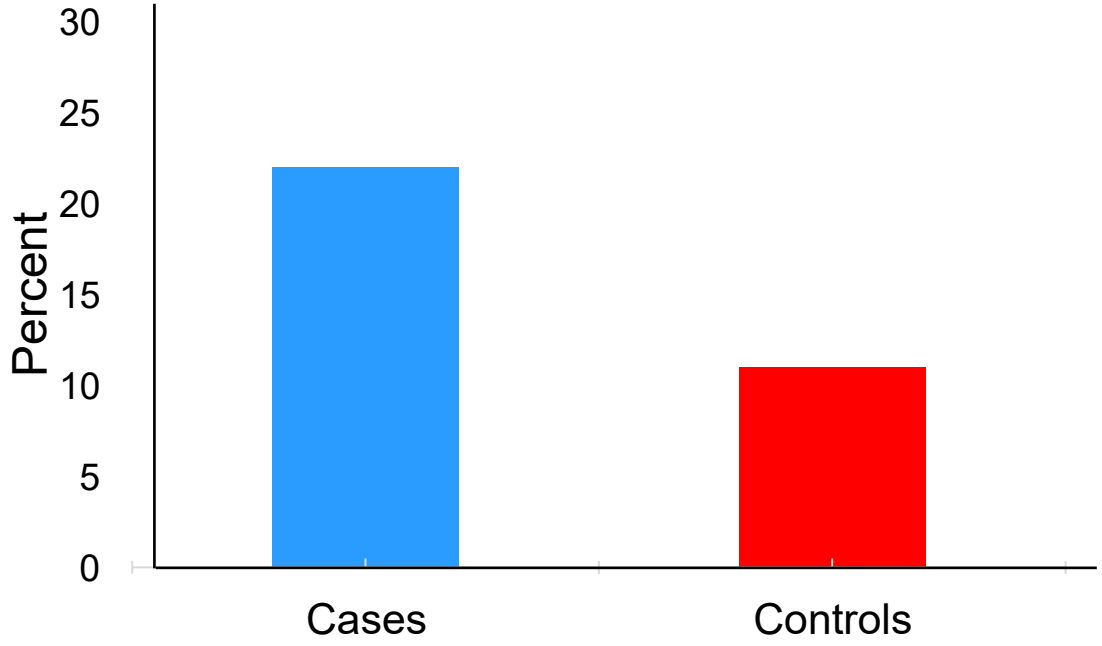
Conditional Logistic Regression Model for MABC Acquisition

	Adjusted Odds Ratio (95% CI)	P value
Independent predictors		
Post-transplant ventilator ≥2 days	2.46 (1.29 – 4.72)	<0.01
Confounding variables		
Ventilator immediately prior to transplant	3.24 (0.64 – 16.48)	0.16
CMV mismatch (donor + / recipient - serology)	1.53 (0.76 – 3.08)	0.24
Number of days in hospital between transplant and index date	1.02 (0.99 – 1.05)	0.20
End-match lung allocation score	1.00 (0.98 – 1.03)	0.73
Idiopathic pulmonary fibrosis	0.52 (0.26 – 1.05)	0.07
≥14 days of azithromycin between transplant and index date	0.21 (0.04 – 1.07)	0.06

The variable bilateral lung transplant was eliminated during backward elimination.

Outcomes

Death ≤1 year after transplant

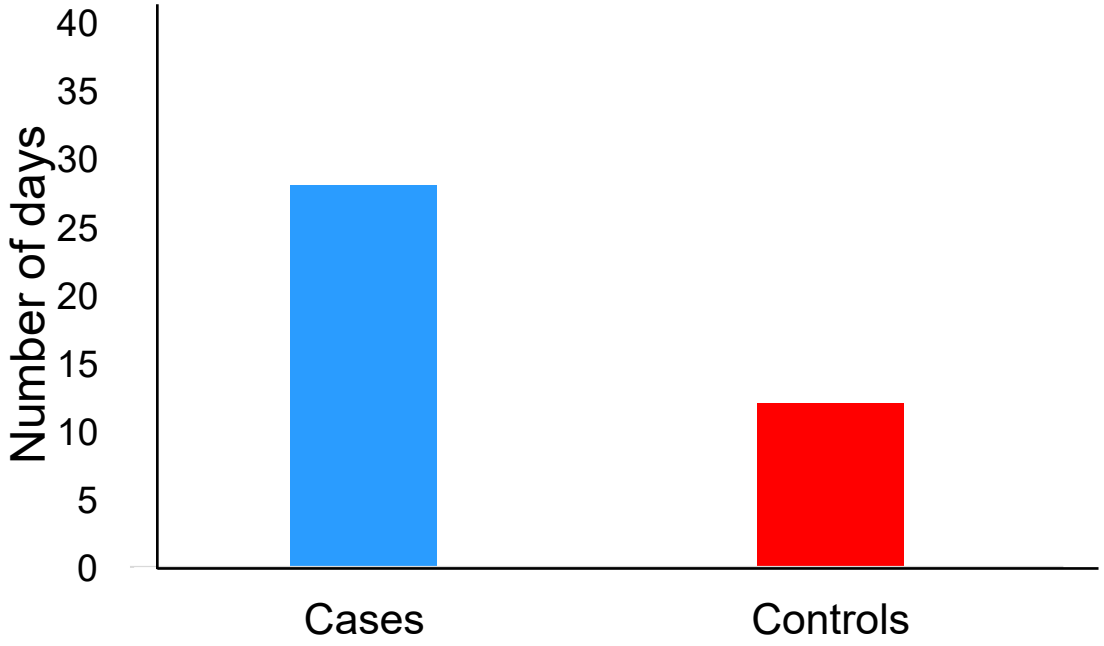


22% of cases
17/79 deaths

11% of controls
27/237 deaths

P = 0.03

Days in hospital between index date and one year after transplant



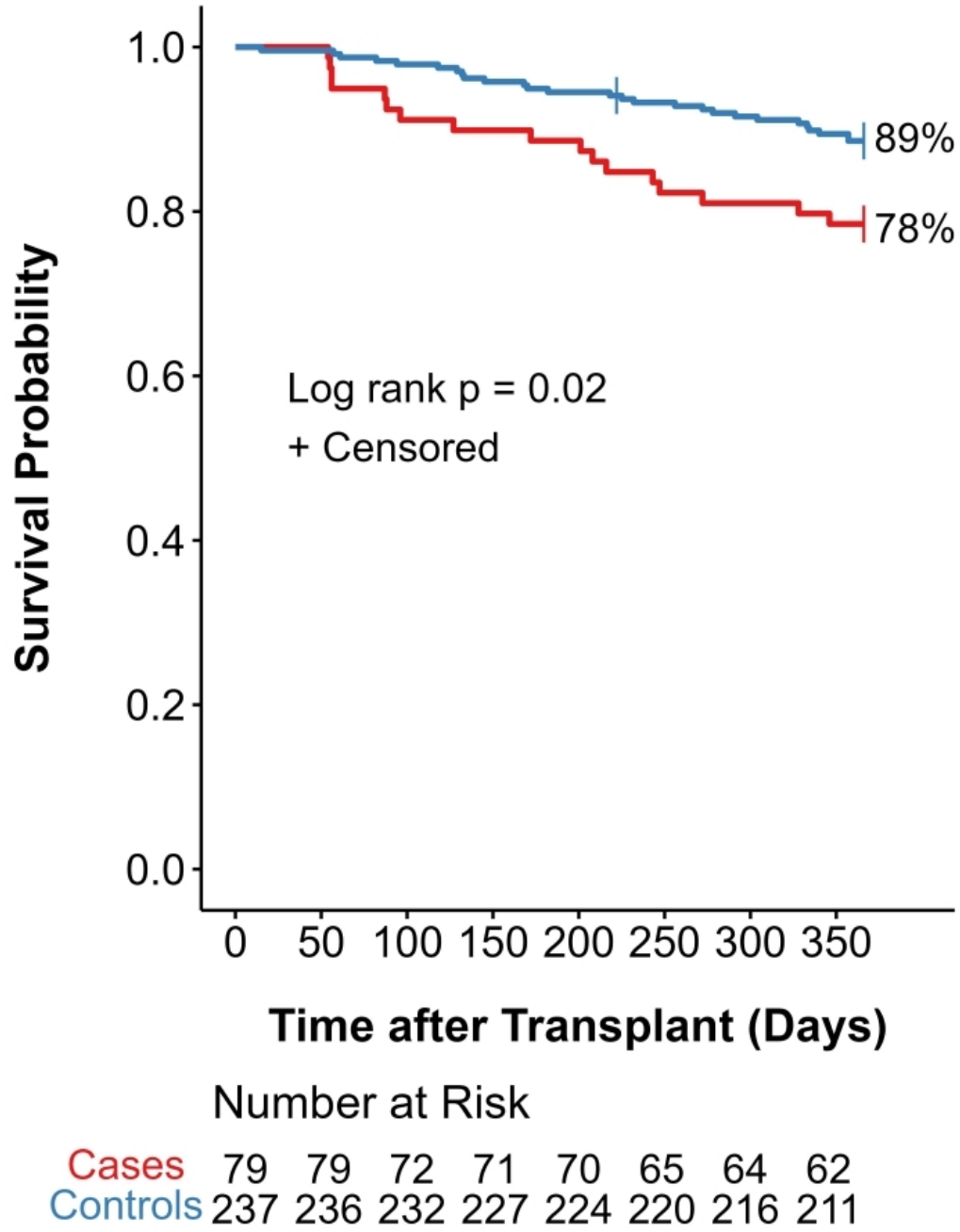
Median 28 days
IQR 12 - 54

Median 12 days
IQR 4 - 34

P = 0.01

Survival Curve

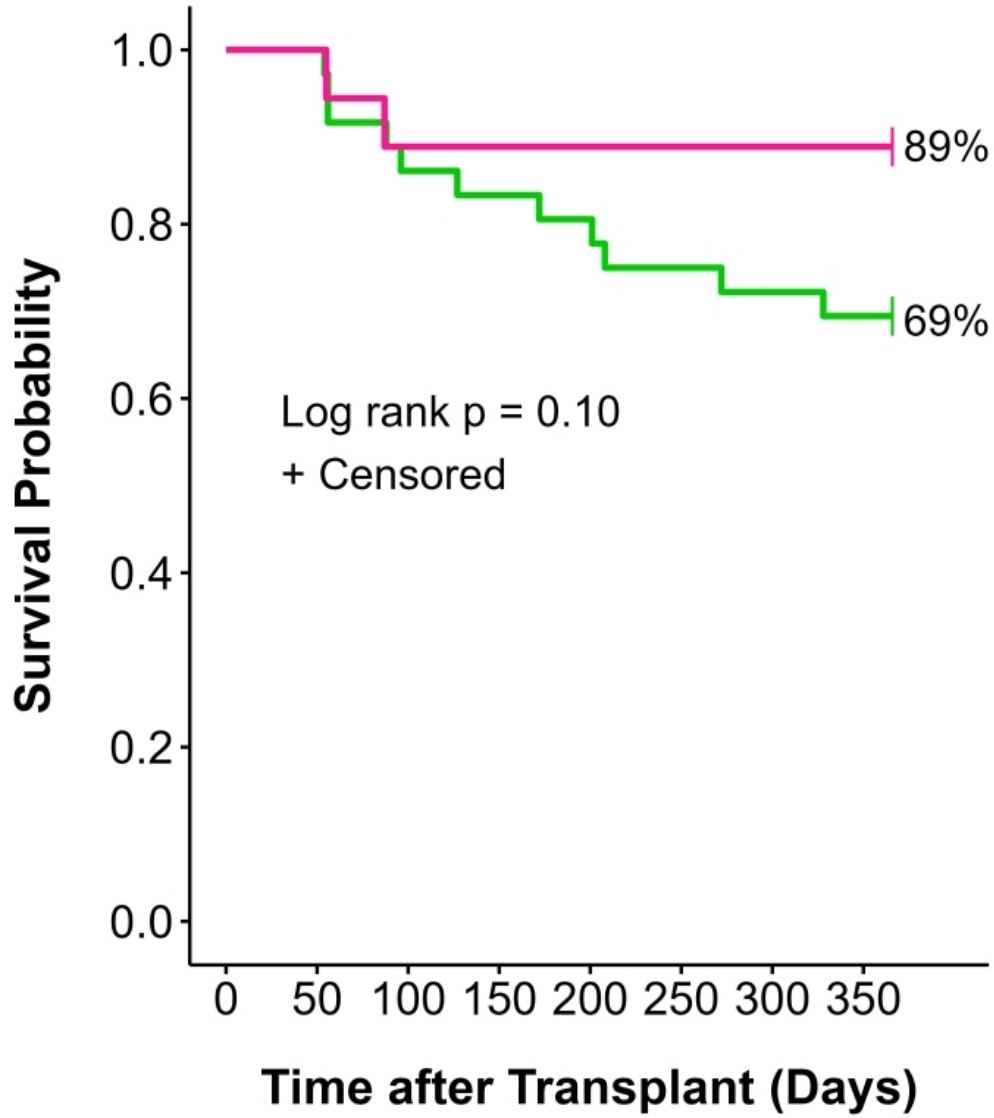
Comparing MABC cases and controls



Duke Center for Antimicrobial Stewardship and Infection Prevention

Survival Curve

Cases stratified by subspecies



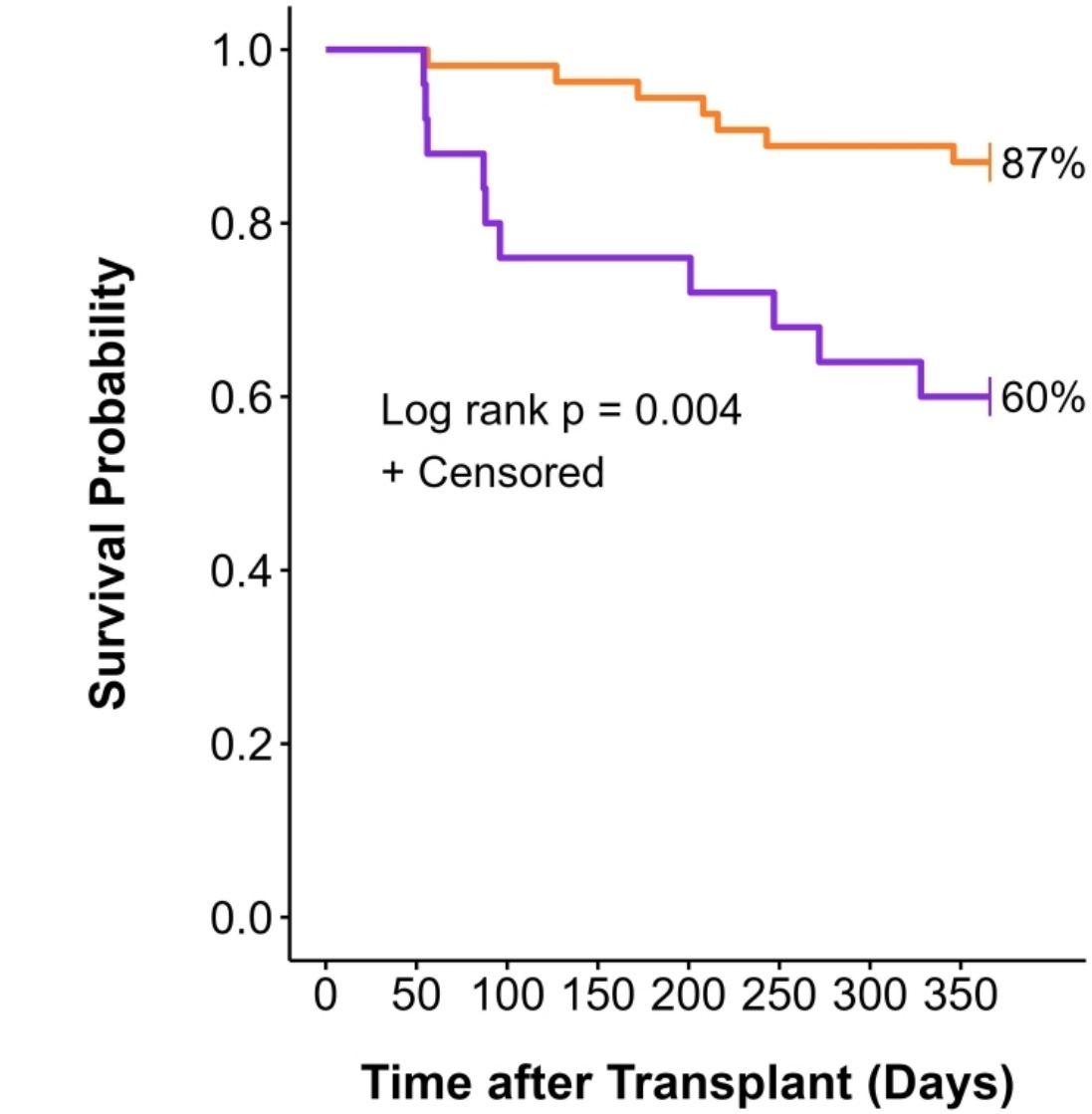
Number at Risk

Subsp. *abscessus*	36	36	31	30	29	27	26	25
Subsp. *massiliense*	18	18	16	16	16	16	16	16

Duke Center for Antimicrobial Stewardship and Infection Prevention

Survival Curve

Cases stratified by specimen site



Number at Risk

No Extrapulm	54	54	53	52	51	48	48	47
Any Extrapulm	25	25	19	19	19	17	16	15

Duke Center for Antimicrobial Stewardship and Infection Prevention

Discussion

- ≥2 days of post-transplant mechanical ventilation is an independent predictor of MABC acquisition

- MABC acquisition is associated with increased post-transplant mortality

Discussion

- ≥2 days of post-transplant mechanical ventilation is an independent predictor of MABC acquisition
  - Likely a surrogate for a complicated post-operative course
  - Increased exposure to water and aerosols colonized with MABC
- MABC acquisition is associated with increased post-transplant mortality

Park J, et al. *Clin Infect Dis.* 2017; 64(3):301-308
Sfeir M, et al. *Open Forum Infect Dis.* 2018;5(2):ofy022

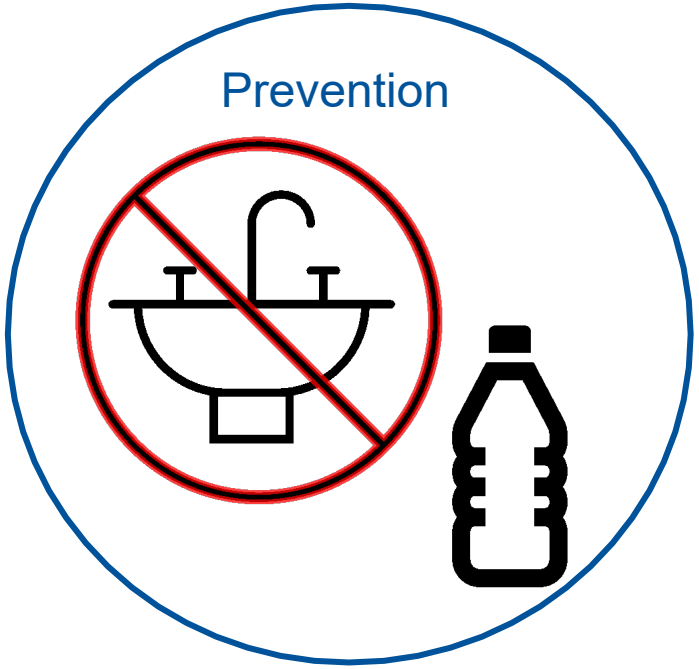
Discussion

- ≥2 days of post-transplant mechanical ventilation is an independent predictor of MABC acquisition
  - Likely a surrogate for a complicated post-operative course
  - Increased exposure to water and aerosols colonized with MABC
- MABC acquisition is associated with increased post-transplant mortality
  - Especially for patients with M. *abscessus* subsp. *abscessus* or extrapulmonary disease

Park J, et al. *Clin Infect Dis.* 2017; 64(3):301-308
Sfeir M, et al. *Open Forum Infect Dis.* 2018;5(2):ofy022

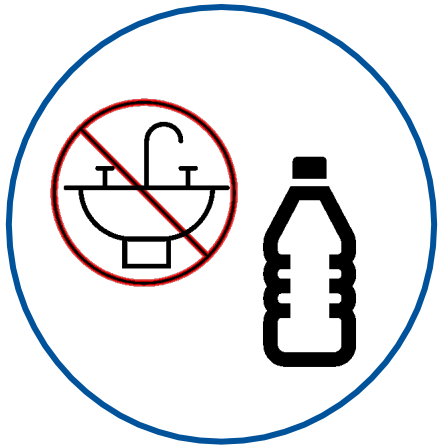
Next Steps

- Vital that hospital prevention programs focus on both prevention and surveillance of NTM



Prevention

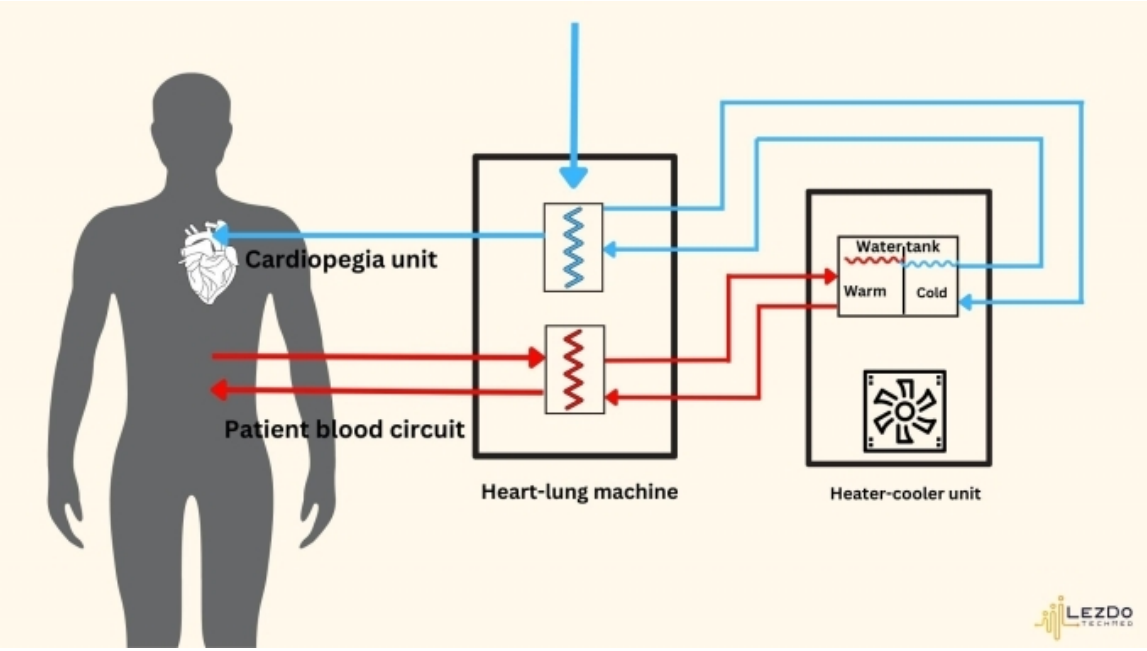
- Hospitals with endemic NTM should ensure effective water management programs
  - Tap water avoidance
  - Use of highly-filtered tap water
  - Water engineering strategies



CDC: Healthcare-Associated Infections – “Reduce Risk from Water.” 2019

Prevention

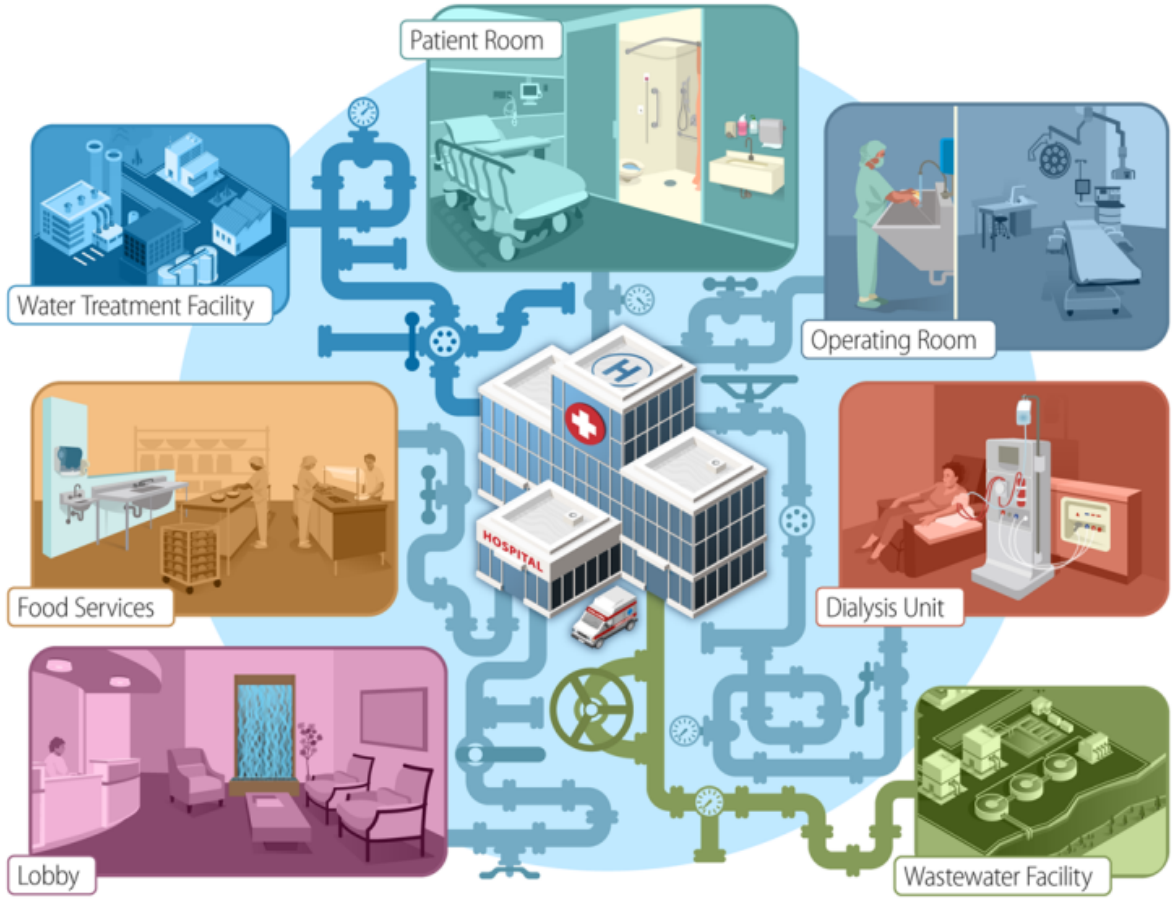
- Heater-cooler unit (HCU) associated NTM



LezDo TechMed. 3T Heater-Cooler Infection: The Unseen Threat in Surgery.
Sorin Group. Heart Lung Machine. “3T-USA.”
U.S. Food and Drug Administration website. “Heater-Cooler Devices.”

Surveillance

- Careful clinical surveillance for MABC and other NTM is also critical



CDC: Healthcare-Associated Infections – “Reduce Risk from Water.” 2019

Limitations

- Unique aspects of our single-center cohort may limit generalizability to other lung transplant recipients and hospitals
  - MABC outbreak
  - Majority of cases caused by two primary outbreak clones
- Pulmonary colonization in the absence of invasive infection

Conclusion

- In this large case-control study, post-transplant ventilator duration was associated with MABC acquisition
  - Increased hospital days and mortality
- *M. abscessus* subspecies *abscessus* and presence of extrapulmonary disease appeared to increase mortality

Additional Data

Characteristics of *Mycobacterium abscessus* complex cases

	All MABC Cases (N=79)
Time to isolation post-transplant, median (IQR), days	33 (11 – 59)
Total number of positive cultures, median (IQR)	3 (1 – 6)
First positive culture was pulmonary	70 (89)
First positive culture was extrapulmonary	9 (11)
Any positive pulmonary culture	74 (94)
MABC culture clearance within 1-year post-transplant	68/74 (92)
Any positive extrapulmonary culture	25 (32)
Positive pulmonary and extrapulmonary culture	20 (25)
Received antibiotics targeting MABC	59 (75)
Did not receive antibiotics targeting MABC	20 (25)
MABC thought to represent pulmonary colonization	18/20 (90)
Diagnosed post-mortem	2/20 (10)
Subspecies *abscessus*	36 (46)
Subspecies *massiliense*	18 (23)
Subspecies *bolletii*	1 (1)
Subspecies unknown	24 (30)

Data are presented as n (%) or n/N (%).
Abbreviations: MABC, Mycobacterium abscessus complex

Duke Center for Antimicrobial Stewardship and Infection Prevention

Breakdown of First Positive Culture

- Pulmonary (70 total patients):
  - 67 BAL
  - 2 Sputum
  - 1 ETS/ETA

- Extrapulmonary (9 total patients):
  - 5 Blood
  - 4 Pleura

Breakdown of All Positive Culture

- Any Pulmonary Cultures (74 total patients):
  - 73 BAL
  - 12 Sputum
  - 4 ETS/ETA

- Any Extrapulmonary Cultures (25 total patients):
  - 14 Blood
  - 11 Pleura
  - 14 Other tissue or body fluid

Additional Culture Data

- 54 (68%) patients had only positive pulmonary cultures (no positive extrapulmonary)
  - 100% of these patients had a positive culture from a BAL

Additional Culture Data

- Average number of positive cultures
  - Median total number of positive cultures: 3 (IQR 1-6)
  - Median total number of positive pulmonary cultures: 2 (IQR 1-5)
  - Median total number of positive extrapulmonary cultures: 0 (IQR 0-1)

- Median days to first positive culture
  - All cultures: 33 days (IQR 11-59)
  - Pulmonary: 30 (IQR 9-59)
  - Extrapulmonary: 58 (IQR 43-73)