2022.4.9 KATRD 제 133차 춘계학술대회
“Controversies in Respiratory Medicine”

Inhaled Conventional Amikacin for Nontuberculous Mycobacterial Pulmonary Disease: Con

Division of Pulmonology
Department of Internal Medicine
University of Ulsan College of Medicine
Asan Medical Center
Kyung-Wook Jo

1. The localization of the NTM biofilm in the interstitial space

2. The deposition of inhaled drugs according to the size

3. Bronchial obstruction in NTM pulmonary disease

4. Treatment outcome between inhaled and IV amikacin

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Chronic pulmonary disease with *Mycobacterium abscessus* complex is a biofilm infection

Tavs Qvist[1,6], Steffen Eickhardt[2,6], Kasper N. Kragh[2], Claus B. Andersen[3], Martin Iversen[4], Niels Høiby[2,5] and Thomas Bjarnsholt[2]

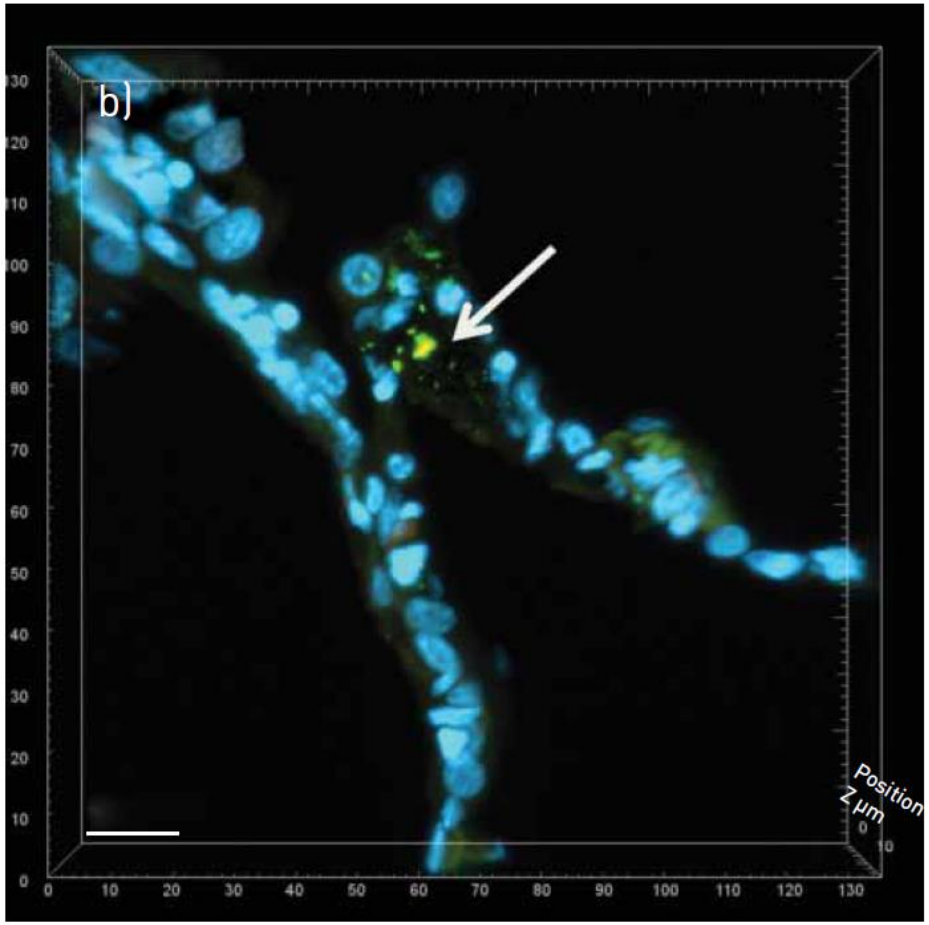
[1]Cystic Fibrosis Centre Copenhagen, Dept of Infectious Diseases, Rigshospitalet, Copenhagen University, Copenhagen, Denmark. [2]Costerton Biofilm Centre, Dept of International Health, Immunology and Microbiology, Copenhagen University, Copenhagen, Denmark. [3]Dept of Pathology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark. [4]Dept of Cardiology, Lung Transplantation Unit, Rigshospitalet, Copenhagen University, Copenhagen, Denmark. [5]Dept of Clinical Microbiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark. [6]These authors contributed equally.

Six patients with cystic fibrosis and *M. abscessus complex* PD

Explanted lung due to lung transplantation

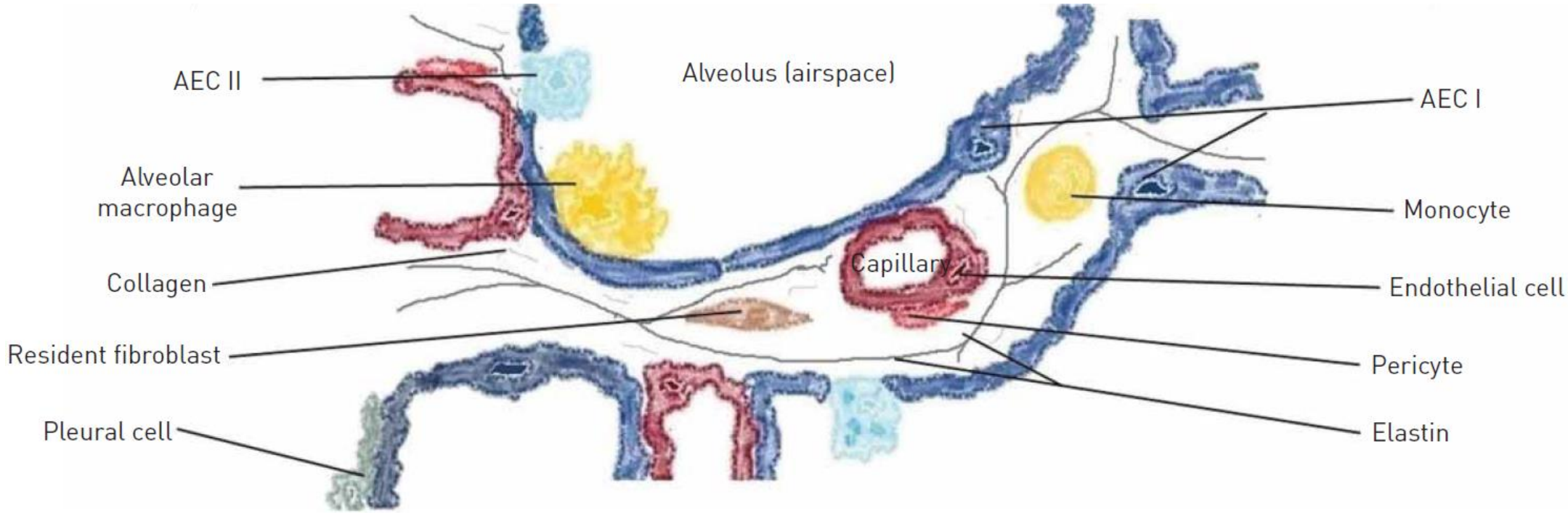
NTM culture and histologic analysis

Eur Respir J 2015;46:1823–1826



M. abscessus complex **in biofilm aggregates and embedded in the interstitial spaces of the respiratory zones of the lung, surrounded by inflammation.**

Eur Respir J 2015;46:1823–1826



Eur Respir J 2015;24:102–114

The epithelial cell membrane

→ the second biological barrier for lung drug delivery.

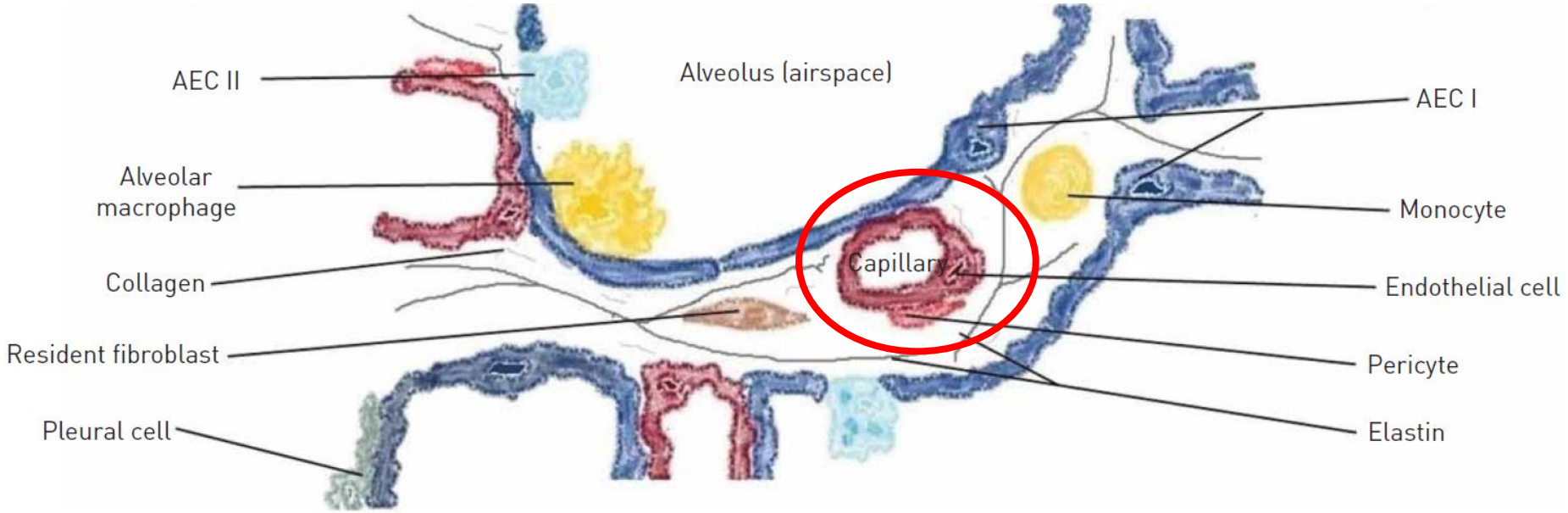
At the alveolar region,

the pneumocytes form a tight alveolar epithelial barrier.

With this barrier,

only particles of <100 nm in size can freely penetrate.

Pharmaceutics 2020;12:1196



***In vivo* localization of the biofilm in the interstitial space**

→ **Intravenous antibiotic treatment should play a prominent role in *M. abscessus complex* disease management than inhaled antibiotics.**

Eur Respir J 2015;46:1823–1826

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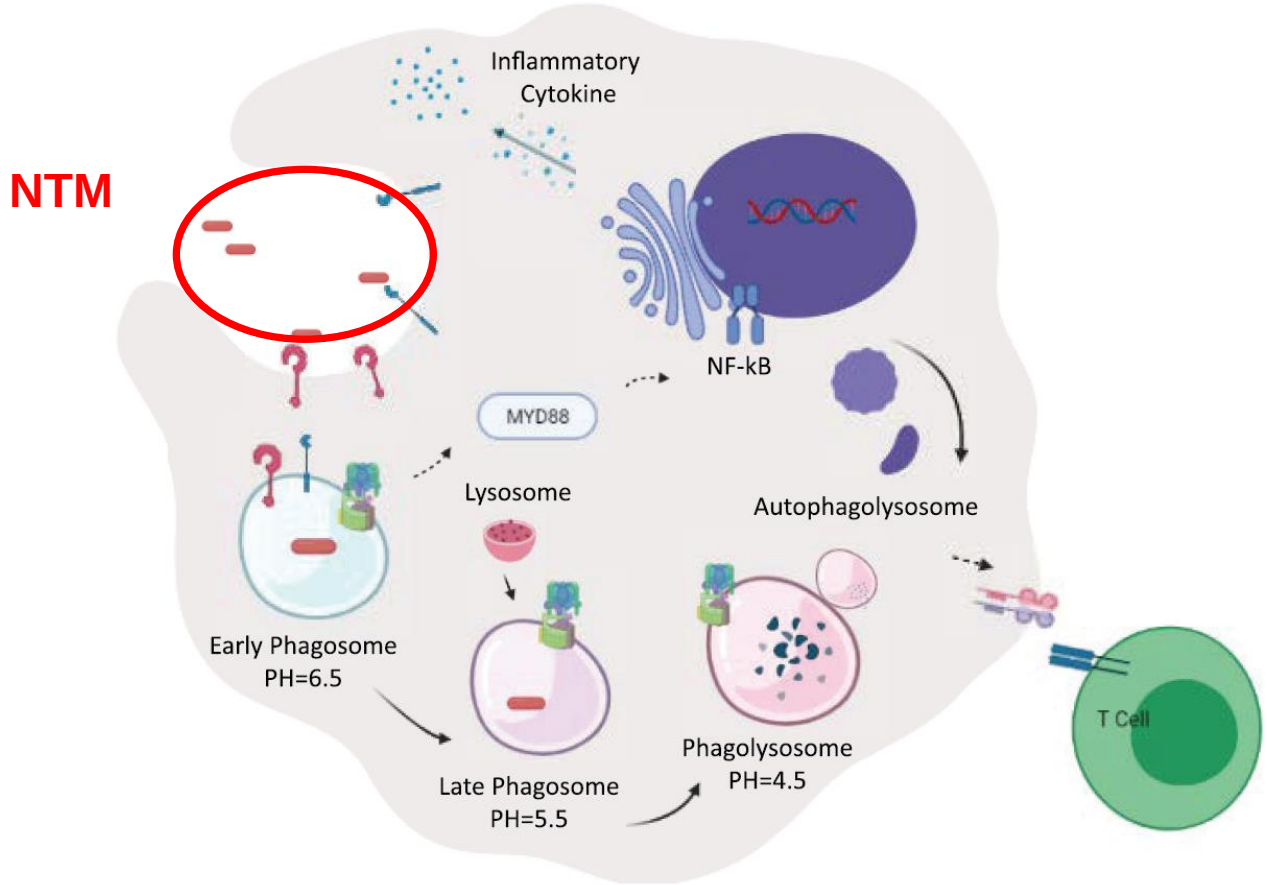
Nontuberculous Mycobacteria, Macrophages, and Host Innate Immune Response

Masoud Shamaei,[a,c] Mehdi Mirsaeidi[b]

[a]Chronic Respiratory Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b]University of Miami, Division of Pulmonary and Critical Care, Miami, Florida, USA
[c]Darabad, NRITLD, Masih Daneshvari Hospital, Tehran, Iran



Infect Immun 2021;89:e00812–20

Original research

Genome-wide association study of non-tuberculous mycobacterial pulmonary disease

Jaeyoung Cho,[1] Kyungtaek Park,[2] Sun Mi Choi,[1] Jinwoo Lee,[1,3] Chang-Hoon Lee,[1] Jung-Kyu Lee,[4] Eun Young Heo,[4] Deog Kyeom Kim,[3,4] Yeon Joo Lee,[5] Jong Sun Park,[3,5] Young-Jae Cho,[5] Ho Il Yoon,[3,5] Jae Ho Lee,[3,5] Choon-Taek Lee ,[3,5] Nayoung Kim,[3,6] Kyu Yeong Choi,[7] Kun Ho Lee,[7,8,9] Joohon Sung,[10,11] Sungho Won,[2,10,11] Jae-Joon Yim[1,3]

What is the bottom line?

- Through a genome-wide association study (GWAS) we identified a putatively significant locus on chromosome 7p13, rs849177, which is possibly associated with susceptibility to NTM-PD in Korean populations by altering the expression levels of the proapoptotic *STK17A* gene.

Impairing apoptosis of

NTM-infected macrophage

Thorax 2021;76:169–177

Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT)

A Prospective, Open-Label, Randomized Study

Amikacin Liposome Inhalation Suspension (ALIS)

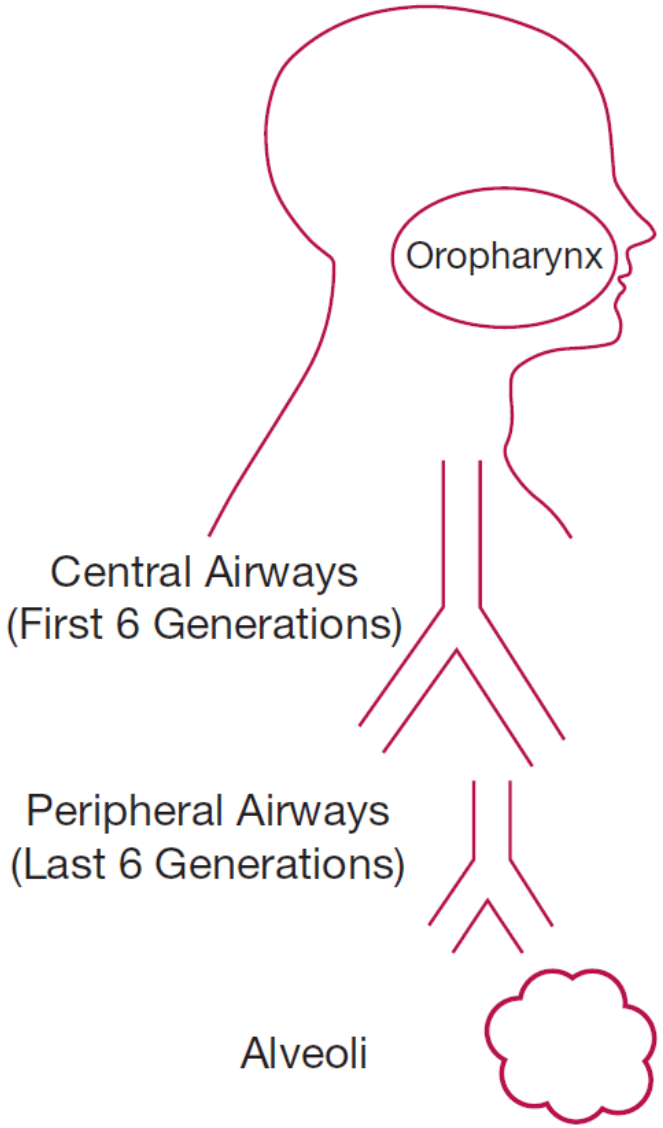
- Amikacin sulfate encapsulated in liposomes for inhalation delivery

- ALIS increases amikacin uptake into an alveolar macrophage,

a refuge for NTM organisms.

AJRCCM 2018;198:1559–1569

Mass Median Aerodynamic Diameter (MMAD)



Preferential Airway Deposition According to Aerosol Particle Size

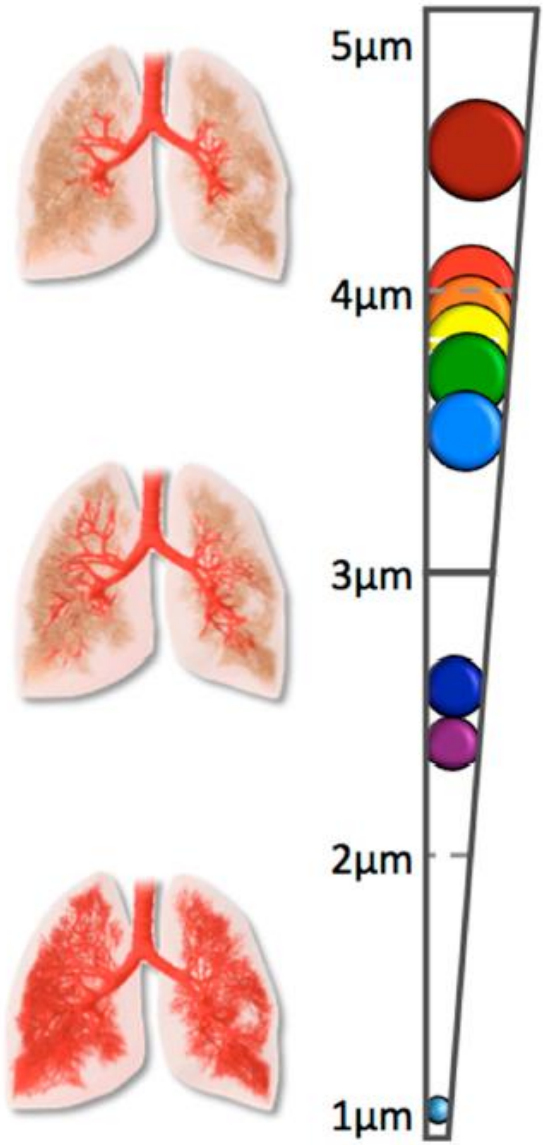
> 10 μm: Impaction in Oropharynx

5-10 μm: Preferential Deposition in Central Airways

0.5-5 μm: Preferential Deposition in Peripheral Airways and Alveoli

< 0.5 μm: Suspension Without Deposition

CHEST 2017;151:740–743



Mass Median Aerodynamic Diameter

Triamcinolone CFC	4.5 µm
Budesonide DPI	4.0 µm
Fluticasone DPI	3.9 µm
Flunisolide CFC	3.8 µm
Mometasone DPI	3.7 µm
Fluticasone HFA	2.4–2.6 µm
Fluticasone CFC	2.4 µm

Extra-Fine Particle Size	
Ciclesonide HFA	1.1 µm
Beclomethasone HFA	1.1 µm

Int. J. Environ. Res. Public Health 2020;17:7287

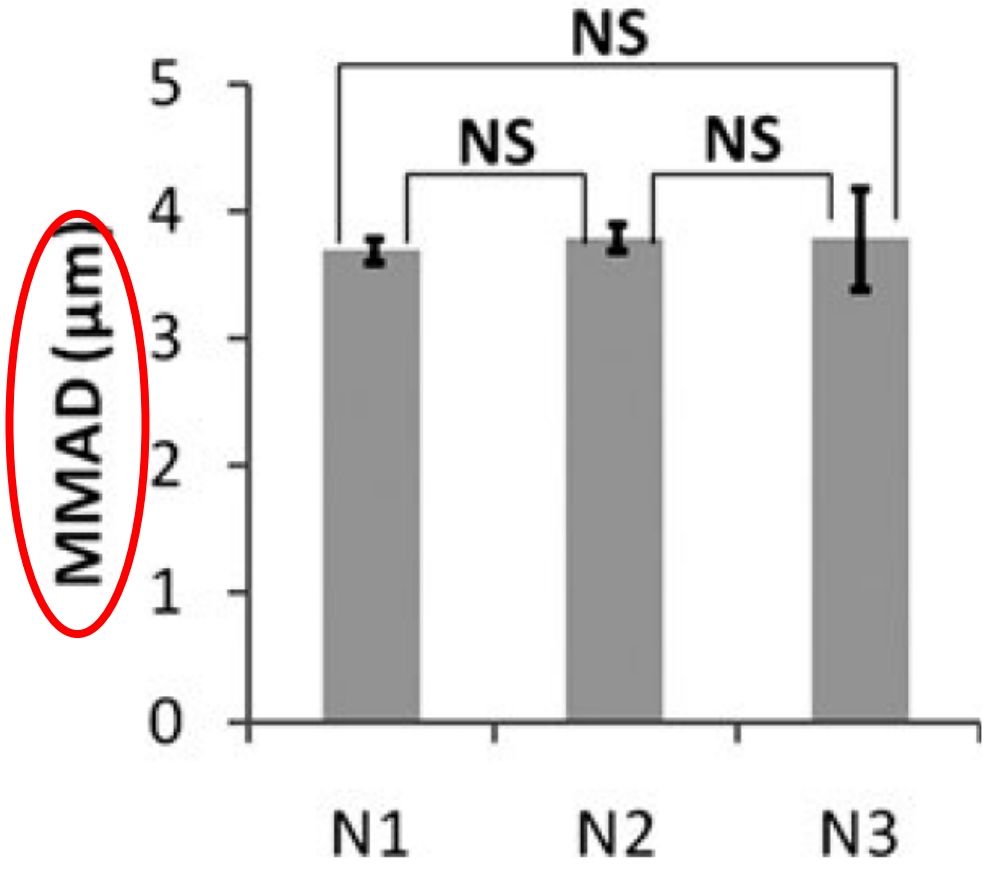
The optimal size is approximately 1–3 μm MMAD to reach the distal lung units.

No available jet nebulizer can consistently produce such a small particle size.

Typical jet nebulizers have a variable particle size of approximately 5 μm MMAD.

CHEST 2017;151:740–743

MMAD of amikacin measured using the three nebulizer delivery system



N1: eFlow rapid nebulizer

N2: Jet nebulizer (Sidestream®)

N3: Jet nebulizer (Sidestream®) with a spacer

*NS, not significant

J Aerosol Med Pulm Drug Deliv 2010;23:389–396

ALIS liposomes are relatively small in size (~300 nm in diameter),

= ~0.3 μm

and have a targeted concentration of amikacin at 70 mg/mL

Drugs 2019;79:555–562

Charge-neutral, highly biocompatible liposomes

The liposomes are taken up by lung macrophages,

allowing intracellular delivery of high levels of amikacin into NTM infected cells.

AJRCCM 2017;195:814–823

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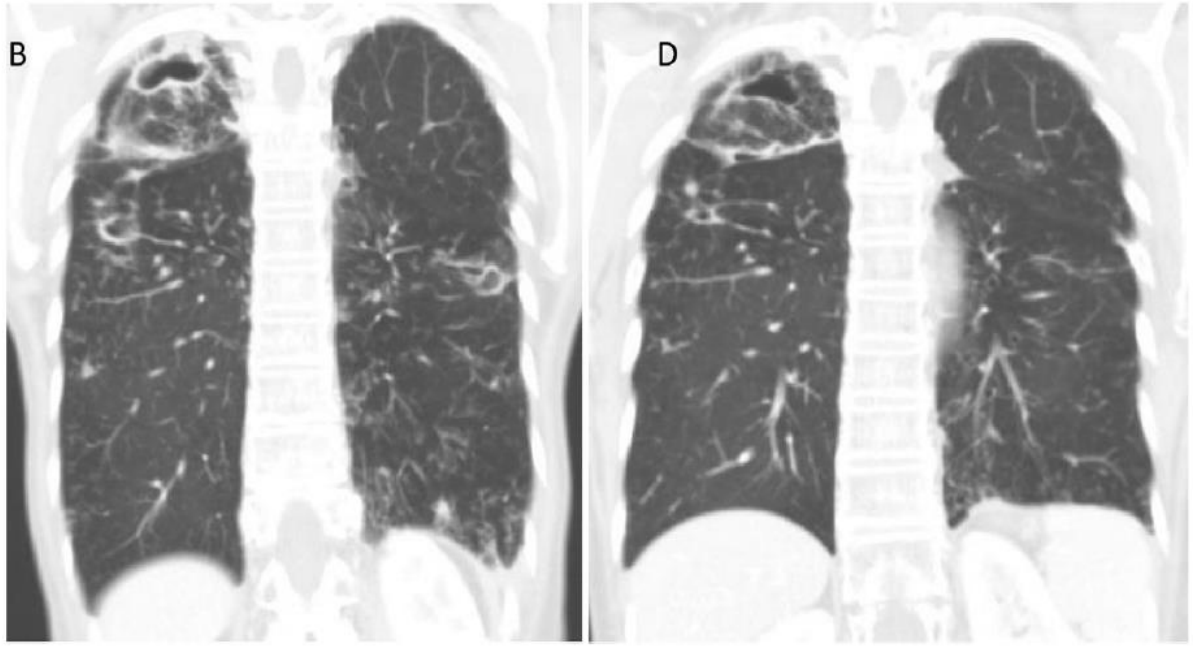
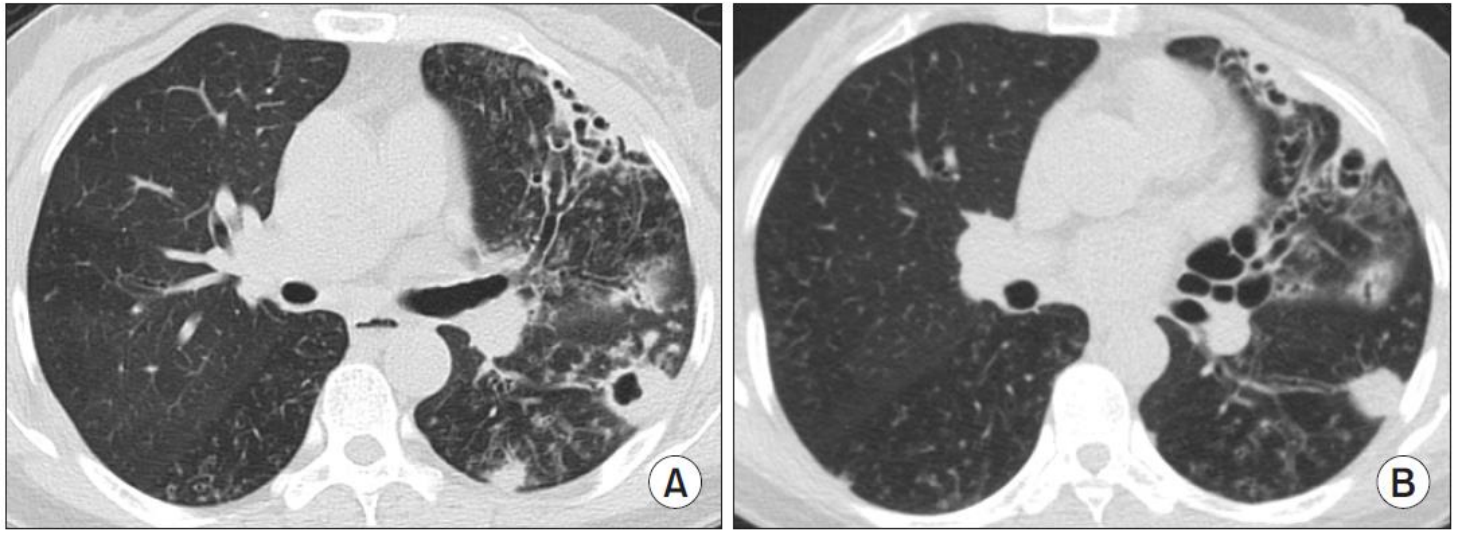


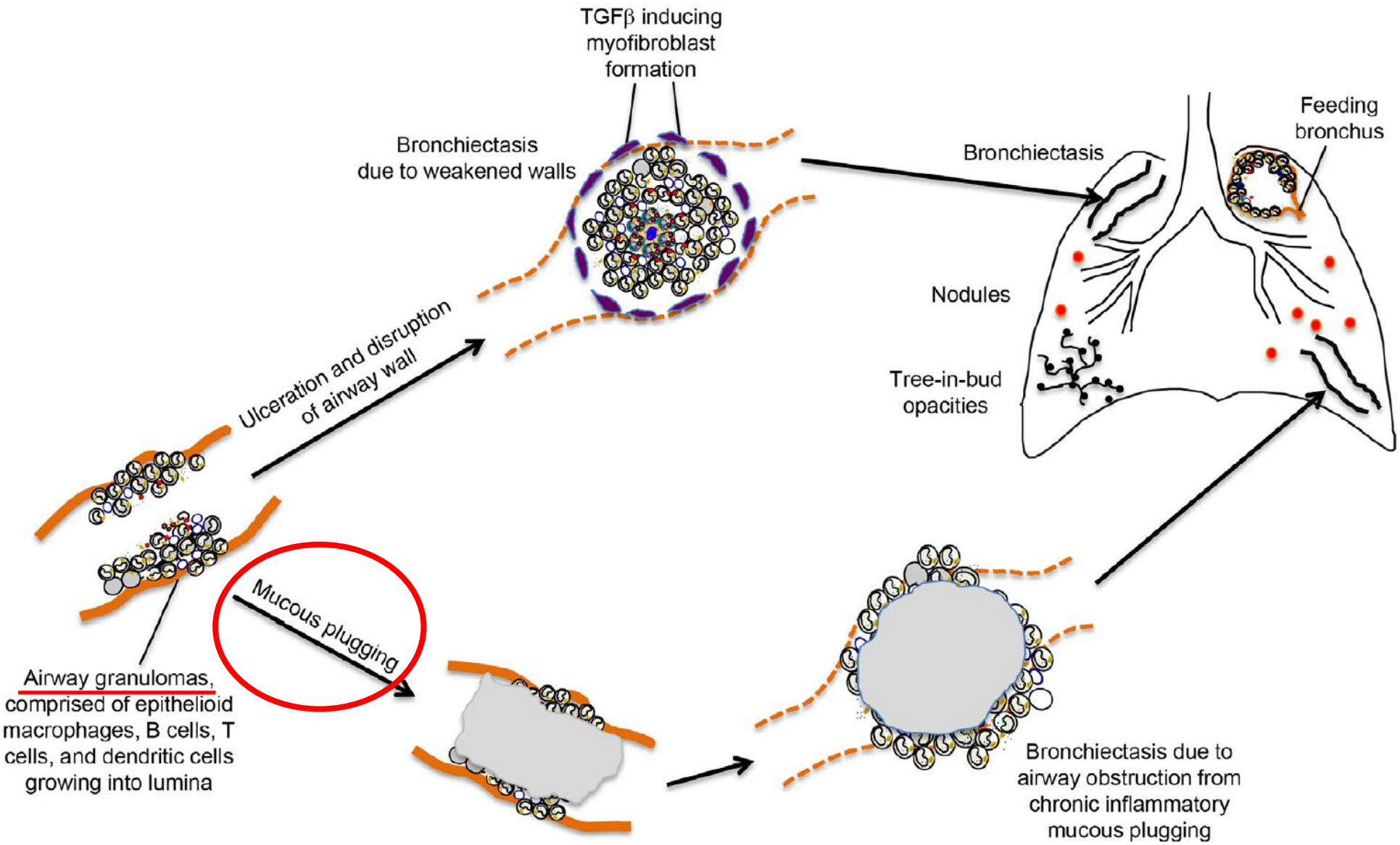
Fibrocavitary type

J Formos Med Assoc 2020;119:S67–S75

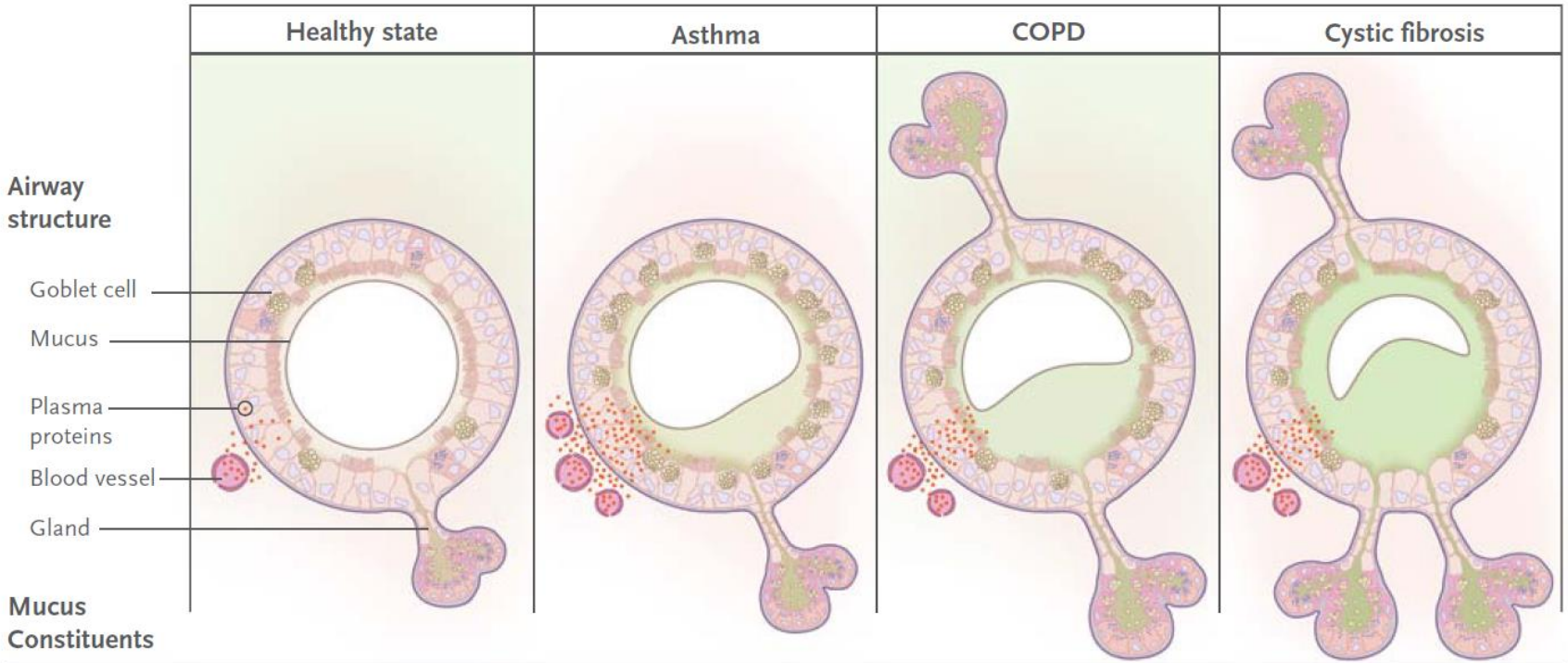


Cavitary nodular bronchiectatic type

Tuberc Respir Dis 2019;82:15–26

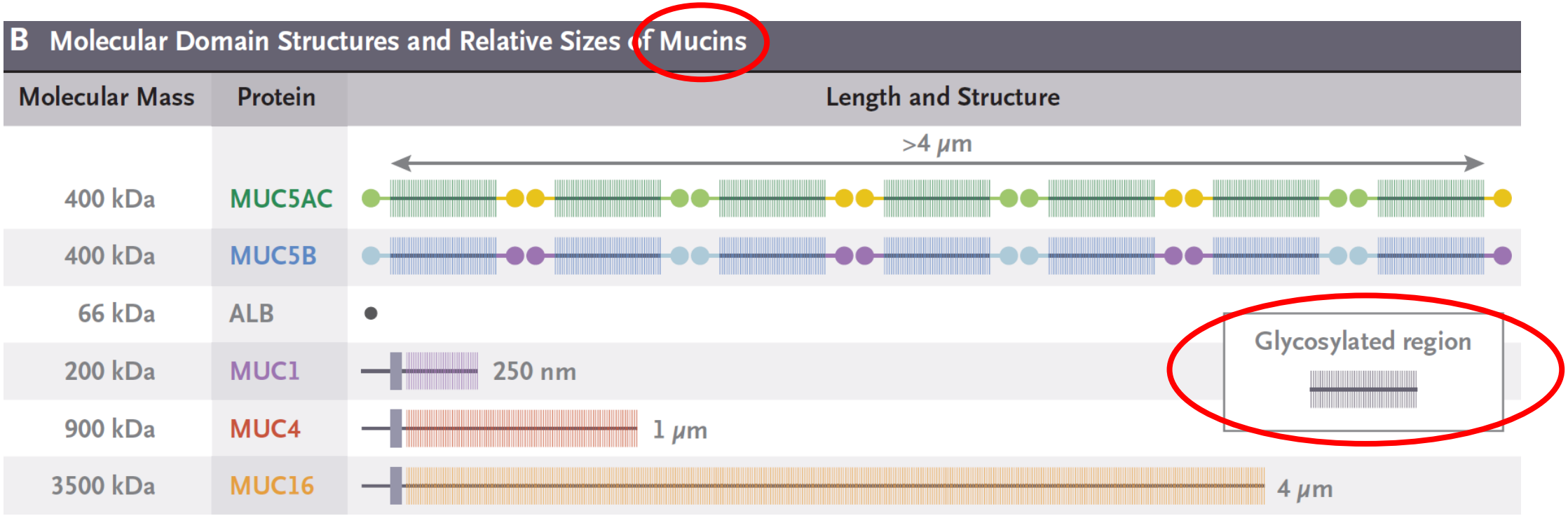


Clin Chest Med 36 2015;36:1–11



Mucus Constituents	Healthy state	Asthma	COPD	Cystic fibrosis
Mucin	X X	X X X X X	X X X X	X X X X
Plasma proteins	X	X X X X	X X	X X
Inflammatory cells	X	X X X	X X X	X X X X X
DNA		X	X X	X X X X X
Actin		X	X X	X X X X X
Bacteria			X X	X X X X X

N Engl J Med 2010;363:2233–2247



The glycosylation domains provide binding sites

capable of trapping most inhaled materials

with a low but sufficient binding affinity to mediate clearance.

N Engl J Med 2019;380:1941–53

Review

Strategies to Overcome Biological Barriers Associated with Pulmonary Drug Delivery

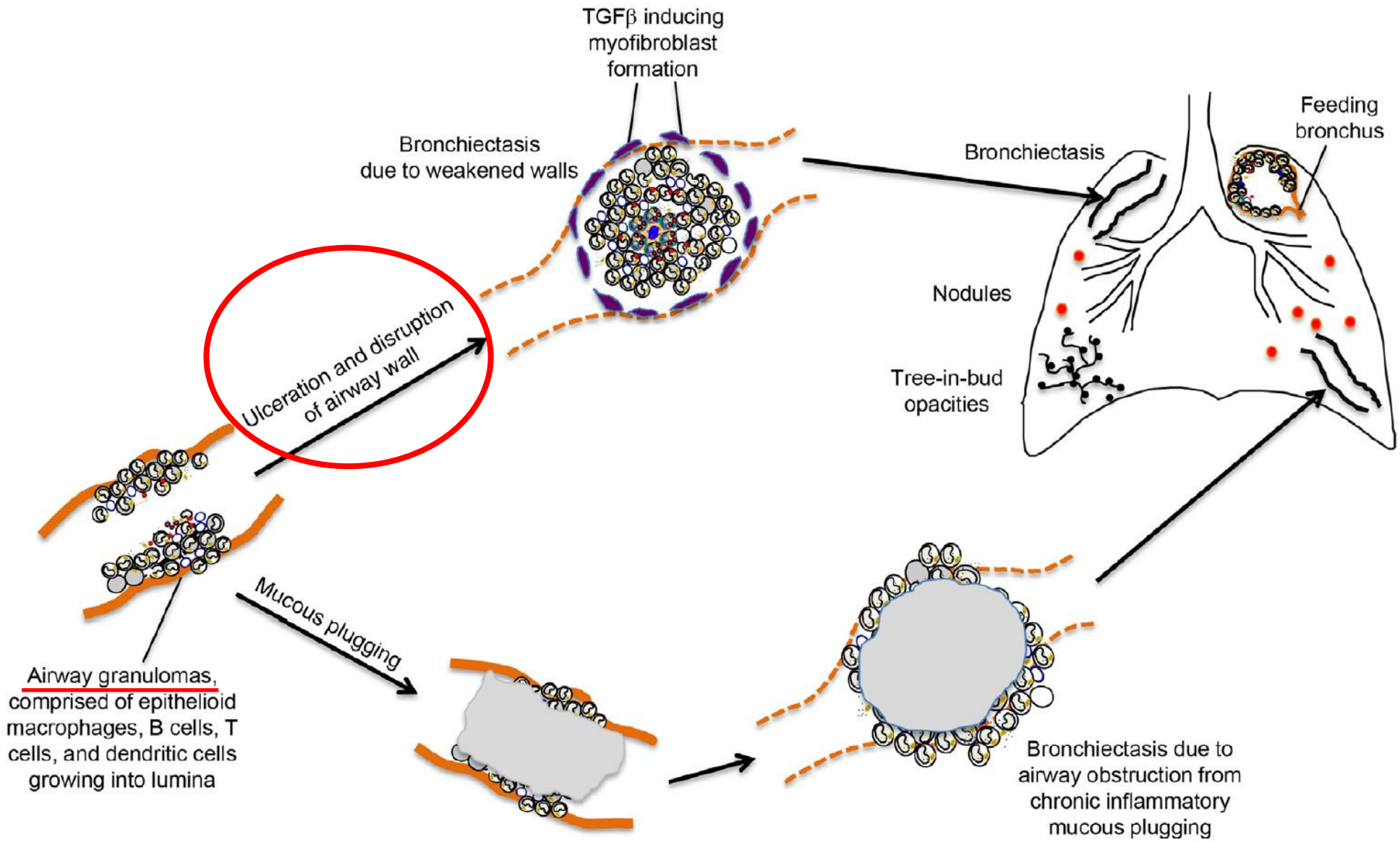
Adam J. Plaunt *, Tam L. Nguyen, Michel R. Corboz, Vladimir S. Malinin and David C. Cipolla

In lung diseases, the mucous of the lower airways

can be overexpressed and/or more thickened, thereby

blocking the access for inhaled drugs to the underlying target tissues.

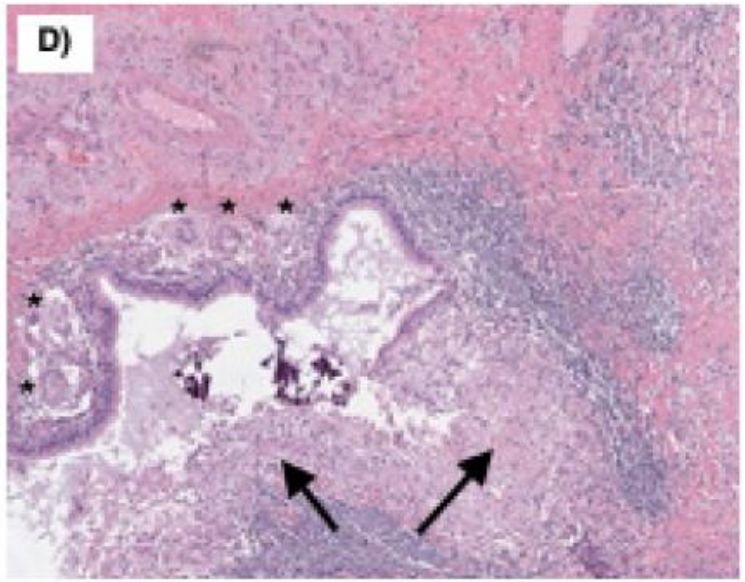
Pharmaceutics 2022;14:302



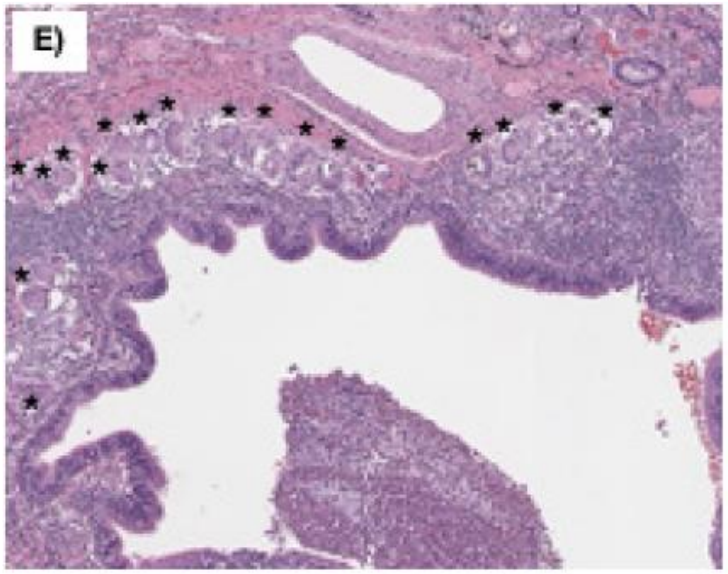
Clin Chest Med 36 2015;36:1–11

Histopathologic Analysis of Surgically Resected Lungs of Patients with Non-tuberculous Mycobacterial Lung Disease: a Retrospective and Hypothesis-generating Study

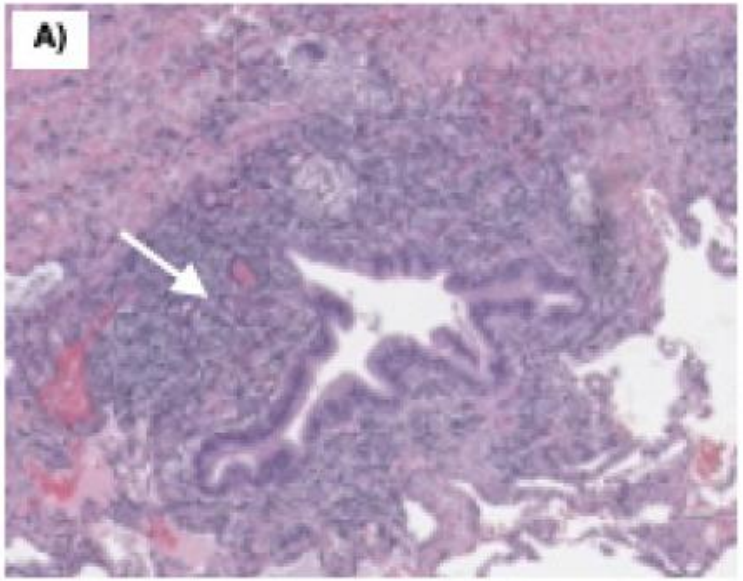
Sangbong Choi[a,1], Kyle J. Potts[b,1], Meghan D. Althoff[c], Guillermo Jimenez[d], Xiyuan Bai[c,e], Kara M. Calhoun[c], Carlyne D. Cool[f,g], and Edward D. Chan[c,e,h,*]



Necrotizing granuloma of the airway



Non-necrotizing granuloma of the airway



Bronchiolitis, infiltration by chronic inflammatory cells

Yale J Biol Med 2021;94:527–535

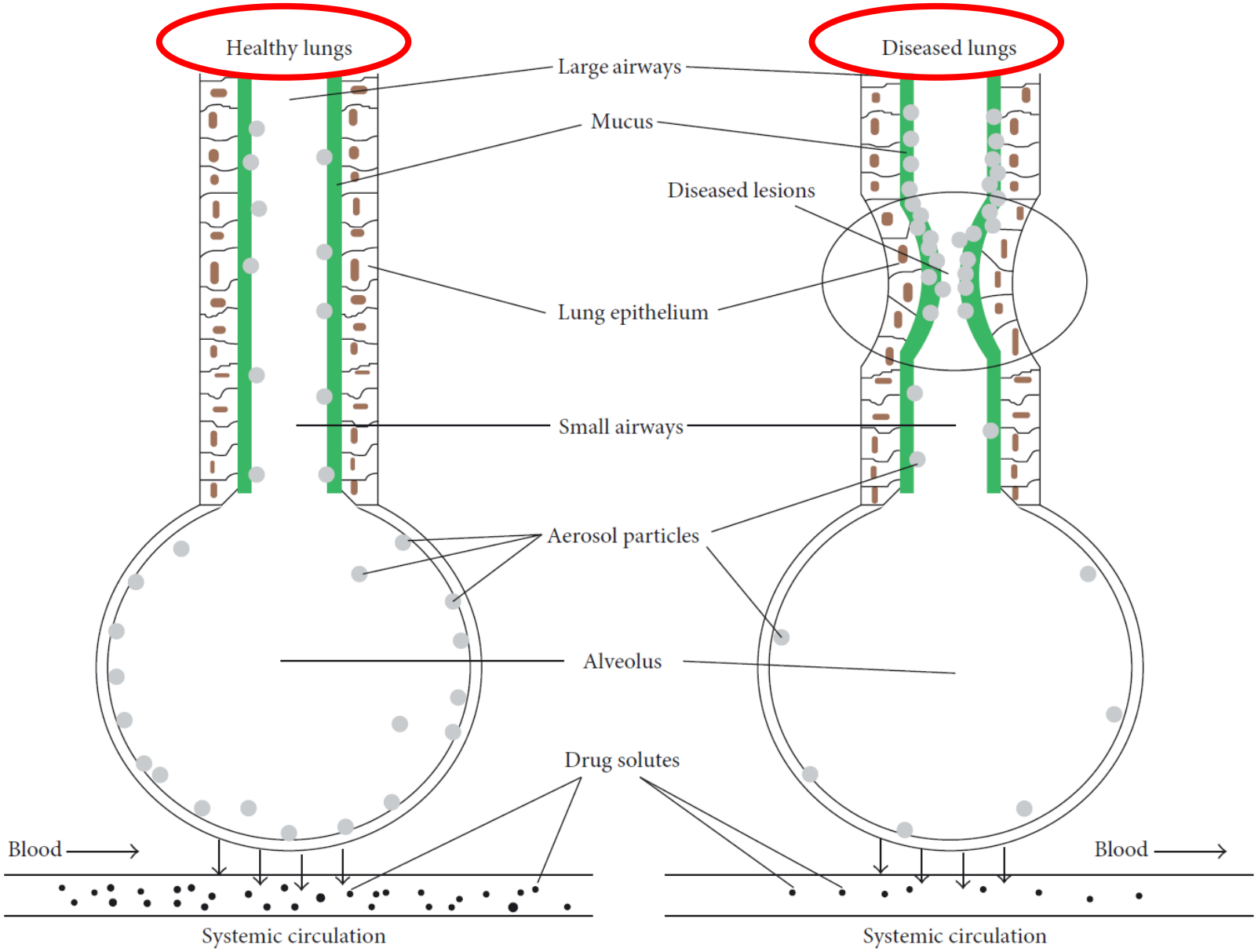
Review

Strategies to Overcome Biological Barriers Associated with Pulmonary Drug Delivery

Adam J. Plaunt *, Tam L. Nguyen, Michel R. Corboz, Vladimir S. Malinin and David C. Cipolla

In lung diseases, the challenge for effective inhaled drug delivery is even more significant due to airway constrictions and excessive mucous production.

Pharmaceutics 2022;14:302



Can Respir J 2018;46:2732017

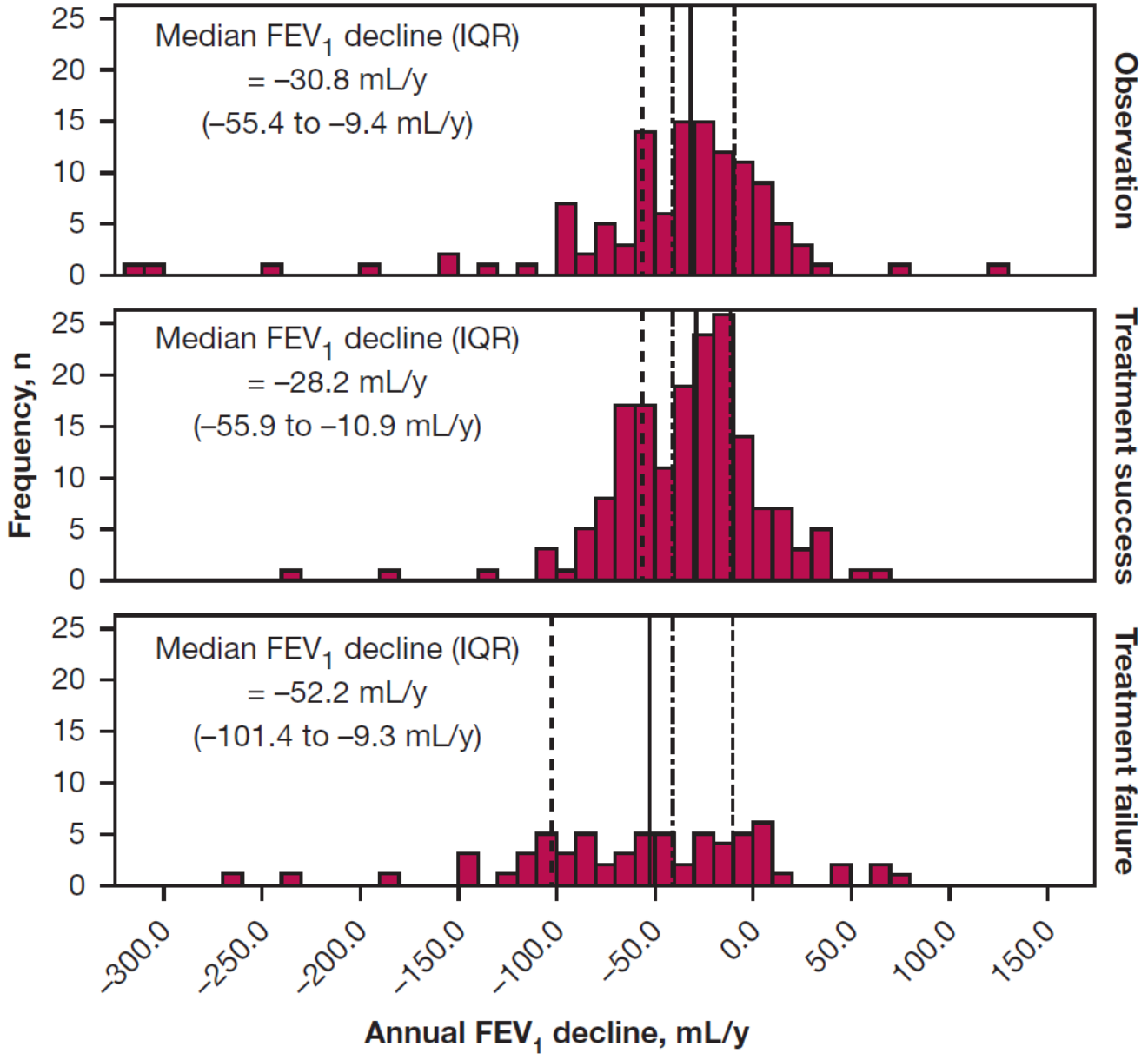
1999–2011,

Samsung medical center

358 NTM–PD

Treatment outcome

and spirometry data



CHEST 2016;150:1222–1232

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Amikacin Inhalation as Salvage Therapy for Refractory Nontuberculous Mycobacterial Lung Disease

Byung Woo Jhun,[a] Bumhee Yang,[a] Seong Mi Moon,[a] Hyun Lee,[a] Hye Yun Park,[a] Kyeongman Jeon,[a] O Jung Kwon,[a] Jungmin Ahn,[b] Il Joon Moon,[b] Sung Jae Shin,[c] Charles L. Daley,[d] Won-Jung Koh[a]

2015.2–2016.6, Samsung Medical Center

Refractory NTM-PD, salvage therapy with amikacin inhalation

Refractory NTM PD in 77 patients

- MABC (n = 48), MAC (n = 20), mixed (n = 9)

→ **Culture conversion: 18%**

Culture conversion in MAC-PD: 15% (3/20)

Antimicrob Agents Chemother 2018;62:e00011–18

Treatment outcome of antibiotics other than inhaled Amikacin in refractory MAC-PD in South Korea

Center	Patients n	Duration	Antibiotics	Main Results
Samsung Medical Center[1]	41	2002–2011	Moxifloxacin	Treatment success in **29%**
Asan Medical Center[2]	51	2004–2012	Clofazimine or Moxifloxaicn or Rifabutin or Linezolid	Treatment success in **15.7%**

[1]***Antimicrob Agents Chemother 2013;57:2281–2285***

[2]***J Infect Chemother 2014;20:602–606***

Outcomes of Inhaled Amikacin-Containing Multidrug Regimens for *Mycobacterium abscessus* Pulmonary Disease

Noeul Kang, MD; Kyeongman Jeon, MD; Hojoong Kim, MD; O Jung Kwon, MD; Hee Jae Huh, MD; Nam Yong Lee, MD; Charles L. Daley, MD; Won-Jung Koh, MD; and Byung Woo Jhun, MD

2015.8–2018.6, Samsung Medical Center

82 treatment naïve patients with MABC-PD

Initial phase, IV amikacin-containing regimen

M. abscesuss-PD: 4-week, *M. massiliense*-PD: 2-week

After discharge, inhaled amikacin (with or without clofazimine)

CHEST 2021;160:436–445

M. abscessus subspecies *abscessus* (n = 36)

Inhaled amikacin: 100% (36/36), for median 18 months

TABLE 3] Treatment Outcome 12 Months After Initiation of Treatment

Outcome	Total (N = 82)	*M massiliense* (n = 46)	*M abscessus* (n = 36)	*P* Value
Symptomatic response				.047
Improved	72 (88)	44 (96)	28 (78)	
Unchanged	4 (5)	1 (2)	3 (8)	
Worsened	6 (7)	1 (2)	5 (14)	
Radiographic response on CT scan				.002
Improved	64 (78)	42 (93)	22 (61)	
Unchanged	7 (9)	3 (7)	4 (11)	
Worsened	11 (13)	1 (2)	10 (28)	
Culture conversion[a]	56 (68)	44 (96)	12 (33)	< .001
Time to conversion, mo	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.9-8.1)	.527
Microbiologic cure[b]	55 (67)	44 (96)	11 (31)	< .001
Cure[c]	53 (65)	42 (91)	11 (31)	< .001
Clinical cure[d]	6 (7)	0 (0)	6 (17)	< .001

CHEST 2021;160:436–445

Impact of Susceptibility to Injectable Antibiotics on the Treatment Outcomes of *Mycobacterium abscessus* Pulmonary Disease

Youngmok Park,[1] Yea Eun Park,[2] Byung Woo Jhun,[3] Jimyung Park,[4] Nakwon Kwak,[4] Kyung-Wook Jo,[2] Jae-Joon Yim,[4] Tae Sun Shim,[2] and Young Ae Kang[1,5]

82 patients with *M. abscessus* subspecies *abscessus* PD

- Asan Medical Center, 2012–2019
- Samsung Medical Center, 2002–2012
- Seoul National University Hospital, 2006–2015
- Severance Hospital, 2012–2018

IV amikacin, median 8.9 weeks (IQR, 4.0–27.1) → **Microbiological cure: 41.5%**

Open Forum Infect Dis 2021;8:ofab125

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TABLE 4 Adverse effects associated with amikacin inhalation-containing regimens

Adverse effect	No. (%) of patients with:		
	Discontinuation	Regimen change[a]	Total
Total	21 (27)	8 (10)	29 (38)
Ototoxicity	11 (14)	4 (6)	15 (19)
Fatigue	6 (8)	1 (1)	7 (9)
Tinnitus	3 (4)	1 (1)	4 (5)
Cough	1 (1)	1 (1)	2 (3)
Hoarseness	0	1 (1)	1 (1)
Nephrotoxicity	0	0	0

[a]Change of amikacin inhalation from 500 mg once daily to 500 mg three times weekly.

Antimicrob Agents Chemother 2018;62:e00011–18

TABLE 5] Adverse Effects Associated With Inhaled Amikacin, Clofazimine, or Linezolid

Adverse Effect	No. (%) of Patients		
	Total	Discontinuation	Dose Reduction
Inhaled amikacin (n = 82)	19 (23)	13 (16)	6 (7)
Ototoxicity	15/19 (79)	12/13 (92)[a]	3/6 (50)
Nephrotoxicity	3/19 (16)	1/13 (8)	2/6 (33)
Hoarseness	1/19 (5)	0	1/6 (17)

CHEST 2021;160:436–445

Adverse effects of intravenous amikacin

Center	Patients n	Species	Nephrotoxicity	Ototoxicity
Four tertiary referral centers[1]	82	*M. abscessus*	**3.7%**	**4.9%**
Asan Medical Center[2]	101	MAC	**2.0%**	**4.0%**

[1]***Open Forum Infect Dis 2021;8:ofab125***
[2]***Clin Infect Dis 2019;68:1870–1876***

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Summary

1. NTM in interstitial space: IV > Inhaled route

2. NTM in the alveolus

    1) Too large MMAD of inhaled amikacin to reach the alveolar space

    2) Blocking of inhaled drug in the airway due to:

        - Excessive mucus

        - Bronchial constriction

3. Treatment outcome and adverse effects

    : Inhaled amikacin does not appear superior to IV amikacin

Review

Pseudomonas Aeruginosa Induced Cell Death in Acute Lung Injury and Acute Respiratory Distress Syndrome

Rushikesh Deshpande [1] and Chunbin Zou [2,*]

Following the infection of the epithelial cells, *P. aeruginosa* causes an upregulation of Fas/Fas ligand on the cell surface, the most important ones that are responsible to trigger apoptosis.

Apoptosis of lung epithelial cells upon *P. aeruginosa* infection forms a crucial part of the host defense against infection

Int. J. Mol. Sci. 2020;21:5356