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2023 기관지확장증 연구회 WORKSHOP

Bronchiectasis, Pathophysiology, Causes and Protracted Bacterial Bronchitis

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김 민 정

Today's Topic ..

Bronchiectasis

- Changes in Definition
- Prevalence and Epidemiology
- Causes and Pathophysiology
- and Protracted Bacterial Bronchitis

Treatment in Children

- Guidelines for Treatment and Management of Children

Bronchiectasis (BE)

- One of the most neglected diseases in respiratory medicine (by ERS)
- A major contributor to chronic respiratory morbidity in affluent and less affluent countries
- Renewed interest in with the increasing appreciation of bronchiectasis in adults, still little research in children

Kendig's disorders of the respiratory tract in children 9th Ed

Definition

- a pathologic state of the conducting airways manifested by **radiographic evidence of bronchial dilation**
- recurrent wet or productive cough and infectious exacerbations
- resulting in generalized airway obstruction and destruction with eventual respiratory failure

Kendig's disorders of the respiratory tract in children 9th Ed

Changes in Definition

- **Irreversible dilatation of airways**
  - **Increased bronchoarterial ratio of greater than 1-1.5**
  - **Multidetector CT (MDCT) with HRCT reconstructions**
  - **At least 2 scans are required, in a “non-acute state”**
- Relatively mild dilatation is frequently observed -> “reversed”

Pediatr Allergy Immunol 2021;32:647-57
J Allergy Clin Immunol 2022;149:867-73

Key symptoms

- Chronic productive or wet cough unresponsive to 4 weeks of antibiotics
- Recurrent (>3 times per year) protracted bacterial bronchitis
- Recurrent pneumonia or lower respiratory tract infections
- Haemoptysis
- Severe asthma
- Digital clubbing
- Persistent chest signs, pneumonia, or chest radiograph changes
- Positive sputum culture for unusual organisms (eg, *Pseudomonas aeruginosa*)
- Respiratory symptoms after infection with certain organisms (eg, *Bordetella pertussis*, adenovirus pneumonia, and *Mycobacterium tuberculosis*)

Suggested diagnosis pathway of bronchiectasis

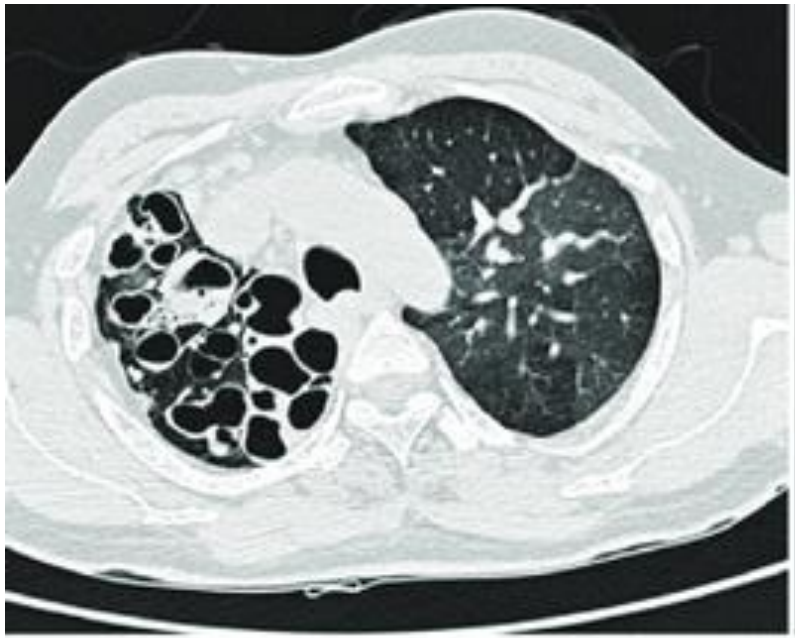
Table 3 Suggested panel of investigations at initial presentation. HRCT imaging confirms the suspected diagnosis with the other suggested investigations to help with further disease assessment including common aetiologies and tools useful in assessing severity

Investigation	Role	Findings
Chest radiograph	Disease assessment	Signs of bronchiectasis ± aetiology Exclude differential diagnoses
HRCT chest scan	Diagnosis	Evidence of bronchial dilatation greater than adjacent artery and any other supporting or diagnostic features
Spirometry	Disease assessment	Presence of airflow obstruction ± reversibility
Total IgE	Disease assessment	Elevated (for ABPA >5000 IU/L)
Sensitization to *Aspergillus fumigatus*	Disease assessment	Elevated serum IgE specific to Aspergillus or positive skin prick test
IgG, IgA and IgM	Disease assessment	Deficient levels suggestive for immunodeficiency syndromes
Sputum bacteriology	Disease assessment	Supporting evidence for chronic airways infection and Mycobacterial infection

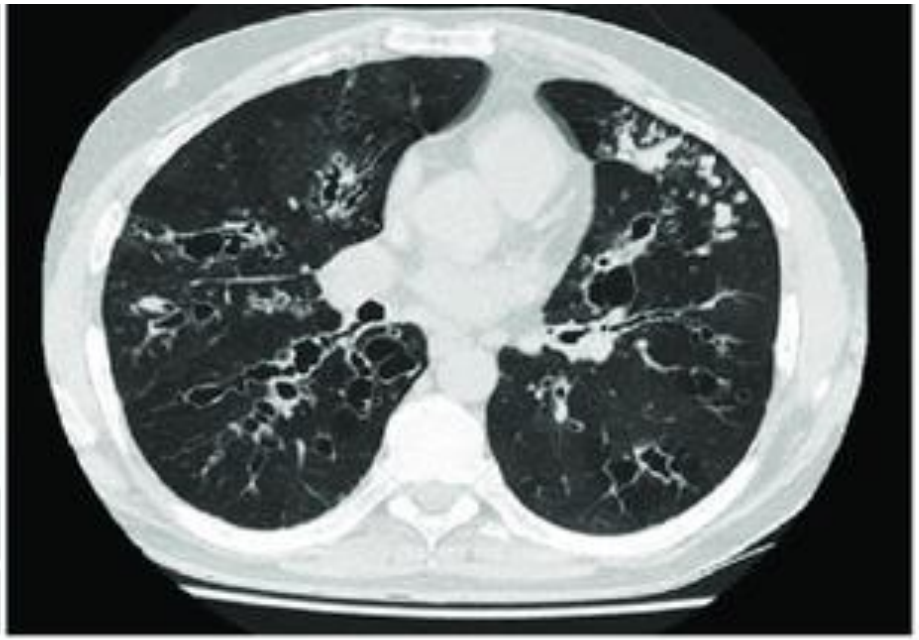
ABPA, allergic bronchopulmonary aspergillosis; HRCT, high-resolution computerized tomography; Ig, immunoglobulin.

Respirology 2019;24(5):413-422

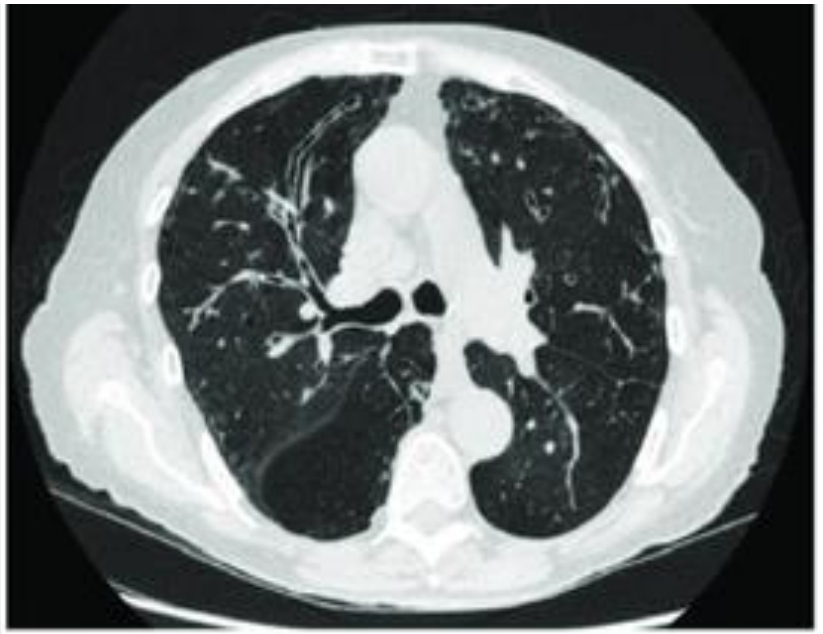
Types of Bronchiectasis



Cystic Bronchiectasis



Varicose Bronchiectasis



Cylindrical Bronchiectasis

Pneumologia 2021;69:209-217

Global incidence and prevalence of BE↑

Table 4 Disease burden in adults

Coding	Author	Country	Prevalence	Time period
ICD (secondary care)	Weycker[37]	USA	52/100 000 adults	1999–2001
ICD (secondary care)	Seitz[5,38]	US	370/10 000 over 65	2000/2007
ICD (secondary care)	Ringshausen[39]	Germany	67/100 000 adults	2013
Read (primary care)	Quint[3]	UK	566.1/100 000 in women and 485.5/100 000 in men	2013
ICD (primary care)	Monteagudo[40]	Catalonia, Spain	35/10 000	2012

Respirology 2019;24(5):413-422

Table 5 Disease burden in paediatrics

Country	Dates	Prevalence	Population
Finland[45]	1983–1992	0.5/100 000	Incidence in hospitalized children in Finland
Australia[46]	2002	1470/100 000	Aboriginal children under 15
USA[47]	Early 2000s	1600/100 000	Alaskan native children
NZ[48]	1998–2000	1/6000	Auckland tertiary referral centre
UK[49]	2005–2007	0.2/100 000	Multicentre registry across UK
Ireland[50]	1996–2006	2.3/100 000	Irish children
United Arab Emirates[51]	1994–1995	13.3/100 000	Paediatric hospital clinic in UAE
NZ	2009–2013	15/100 000	Children living in poverty in NZ, multi-ethnic
Fiji[52]	1985–1989	7/100 000	People native to Fiji
USA[5]	2000–2007	1106 cases per 100 000 people	5% Sample of the Medicare outpatient claims database. 8-Year period prevalence reported

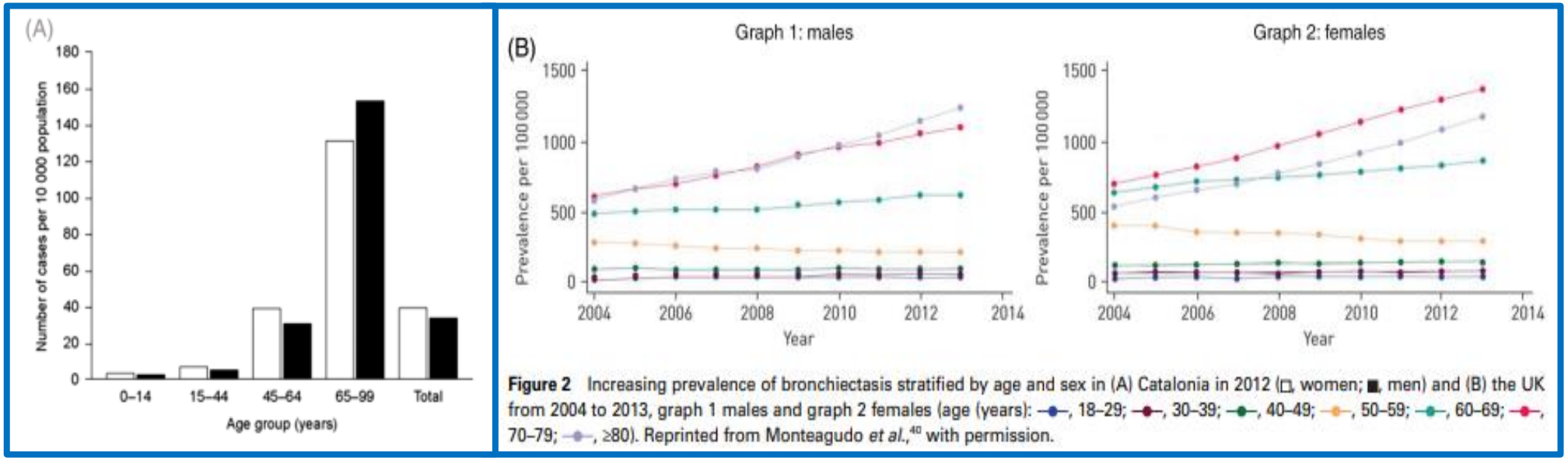


Figure 2 Increasing prevalence of bronchiectasis stratified by age and sex in (A) Catalonia in 2012 (□, women; ■, men) and (B) the UK from 2004 to 2013, graph 1 males and graph 2 females (age (years): —●—, 18–29; —●—, 30–39; —●—, 40–49; —●—, 50–59; —●—, 60–69; —●—, 70–79; —●—, ≥80). Reprinted from Monteagudo *et al.*,[40] with permission.

Respirology 2019;24(5):413-422

TABLE 1 Economic burden of bronchiectasis

Outpatient direct costs	Inpatient direct costs	Advanced disease costs	Indirect costs
Medication costs	Length of stay	Long-term oxygen therapy	Work productivity impairment (absenteeism and presenteeism)
Medical appointments	Intravenous antibiotics	Non-invasive ventilation	Disability and early retirement
Physiotherapy	ICU resources	Lung transplantation	Limitations of daily life
Pulmonary rehabilitation	Inpatient physiotherapy		Caregiver burden
Treatment of exacerbations	Imaging and laboratory exams		
Treatment of complications	Treatment of complications		
Sputum microbiology			
Radiology			
Laboratory exams			

ICU: intensive care unit.

ERJ Open Res 2021;7:00507-2021

Table 1 Summary of the risk factors for development of bronchiectasis in adults by disease category (n = 8608 patients)

Risk factors	Total number	% of total
Idiopathic bronchiectasis	3857	44.8
Post-infective bronchiectasis	2574	29.9
Immunodeficiency	429	5.0
Chronic obstructive pulmonary disease	333	3.9
Connective tissue		
Allergic bronchop aspergillosis		
Ciliary dysfunctio		
Asthma		
Inflammatory bow		
Obstructive		
Aspiration/esoph		
Congenital malfo		
α_1-Antitrypsin de		
Diffuse panbronc		
Pink's disease		
Yellow nail syndr		
Others[†]		

[†]Other aetiolog amyloid (n = 1), s (n = 1), Young's (n = 3), vasculitis fibrosis or cystic fibrosis transmembrane conductance regulator related bronchiectasis (n = 20), systematic disease (n = 47) and other unreported (n = 42).

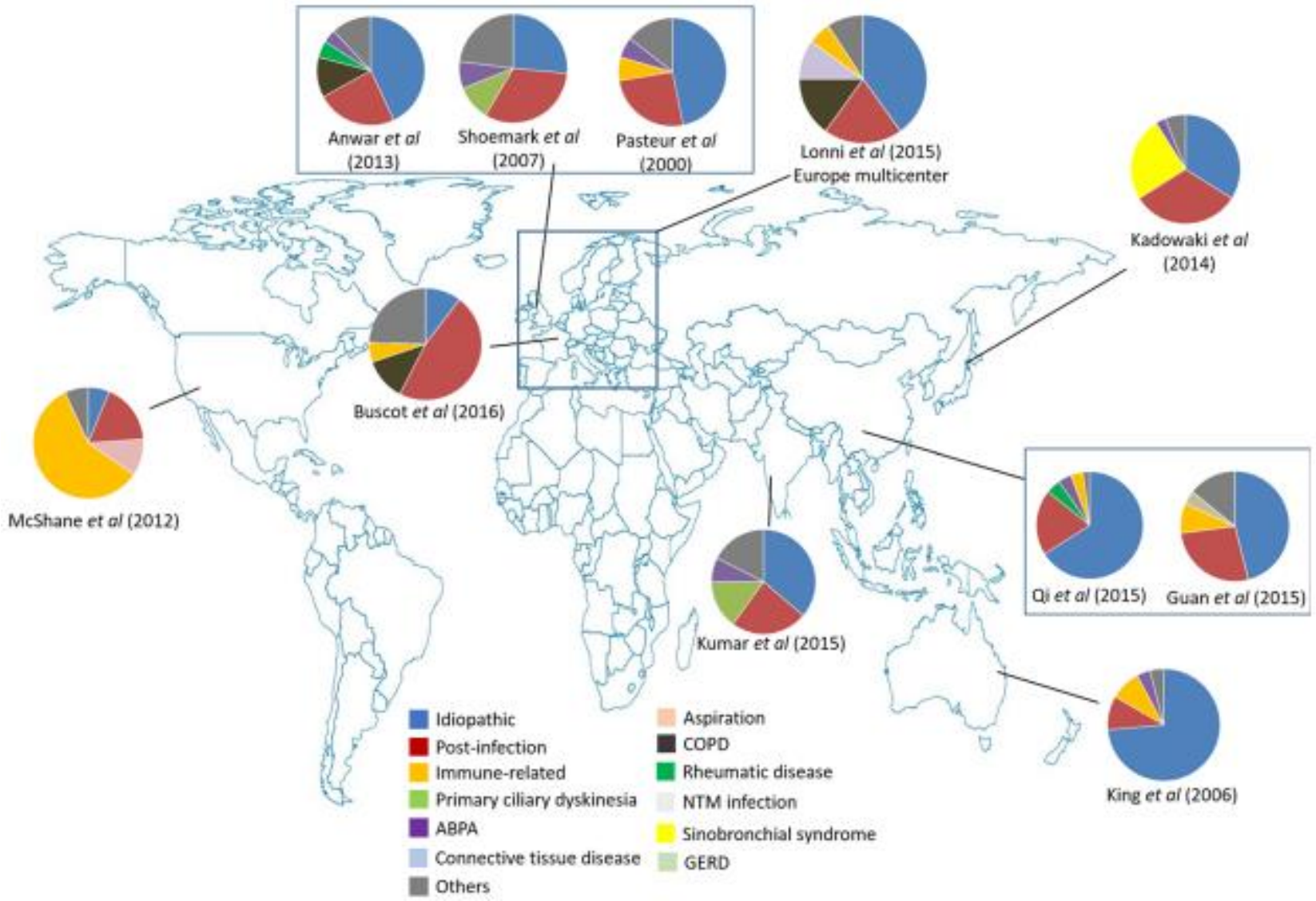
Table 2 Risk factor for development of bronchiectasis in different geographic regions

Risk factors	Asia (n = 8)	Europe (n = 35)	North America (n = 1)	South America (n = 5)	Africa (n = 1)	Oceania (n = 6)	P*
Total	1198	6364	106	308	32	600	
Idiopathic bronchiectasis	709 (59.2%)	2616 (41.1%)	7 (6.6%)	115 (37.3%)	8 (25%)	402 (67%)	<0.001
Post-infective bronchiectasis	273 (22.8%)	1984 (31.2%)	20 (18.9%)	147 (47.7%)	20 (62.5%)	129 (21.5%)	<0.001
Immunodeficiency	37 (3.1%)	337 (5.3%)	18 (17.0%)	6 (1.9%)	0 (0.0%)	31 (5.2%)	<0.001
Chronic obstructive pulmonary disease	1 (0.1%)	329 (5.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	<0.001
Connective tissue disease	33 (2.8%)	252 (4.0%)	30 (28.3%)	6 (1.9%)	0 (0.0%)	5 (0.8%)	<0.001
Allergic bronchopulmonary aspergillosis	26 (2.2%)	181 (2.8%)	1 (0.9%)	1 (0.3%)	0 (0.0%)	14 (2.3%)	<0.001
Ciliary dysfunction	25 (2.1%)	172 (2.7%)	3 (2.8%)	11 (3.6%)	2 (6.3%)	5 (0.8%)	<0.001
Asthma	10 (0.8%)	107 (1.7%)	0 (0.0%)	3 (1.0%)	0 (0.0%)	0 (0.0%)	<0.001
Inflammatory bowel disease	2 (0.2%)	61 (1.0%)	3 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Obstructive	3 (0.3%)	45 (0.7%)	16 (15.1%)	1 (0.3%)	1 (3.1%)	1 (0.2%)	<0.001
Aspiration/esophageal reflux	10 (0.8%)	31 (0.5%)	12 (11.3%)	7 (2.3%)	1 (3.1%)	3 (0.5%)	<0.001
Congenital malformation	8 (0.7%)	25 (0.4%)	1 (0.9%)	3 (1.0%)	0 (0.0%)	0 (0.0%)	<0.001
α_1-Antitrypsin deficiency	0 (0.0%)	23 (0.4%)	12 (11.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	<0.001
Diffuse panbronchiolitis	22 (1.8%)	5 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Pink's disease	0 (0.0%)	9 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (1.8%)	<0.001
Yellow nail syndrome	1 (0.1%)	10 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Others	36 (3.0%)	204 (3.2%)	2 (1.9%)	5 (1.6%)	0 (0.0%)	3 (0.5%)	0.001

*P value with respect to the difference among the studies, the chi-square or Fisher's exact test was used to compare the unique etiologic spectra among different regions when appropriate.

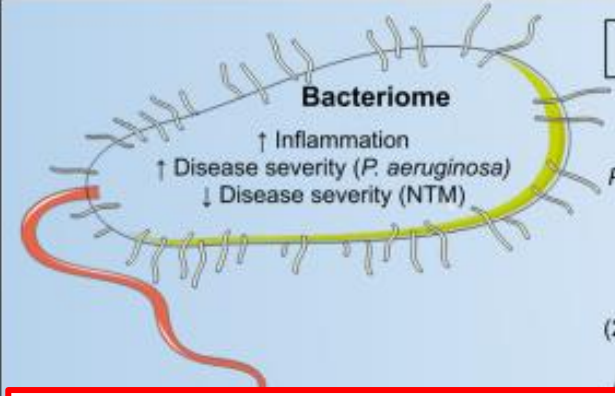
Respirology 2016;21(8):1376-1383

Geographic variation in the epidemiology of BE



BMC Pulm Med 2018;18(1):83

Geographic variation in the microbiology of BE



	Europe – US – Canada		Asia-pacific	
	Adult:	**Paediatric:**	**Adult:**	**Paediatric:**
	US: *P. aeruginosa* (10), NTM (55)	**UK:** *H. Influenzae* (90,91)	**China, Japan & Thailand:** *P. aeruginosa* (57, 58, 37, 61)	**New Zealand:** *H.Influenzae* (41, 42, 85)
	Europe: *P. aeruginosa* (29, 45, 67, 71, 92), *Prevotella* (94), *H. Influenzae* (93)	**Ireland:** *H. influenzae* (89)	**South Korea:** NTM (97) **Australia:** *H. Influenzae* (98, 99)	**Australia:** NTHi (87), *H. Influenzae* (88)

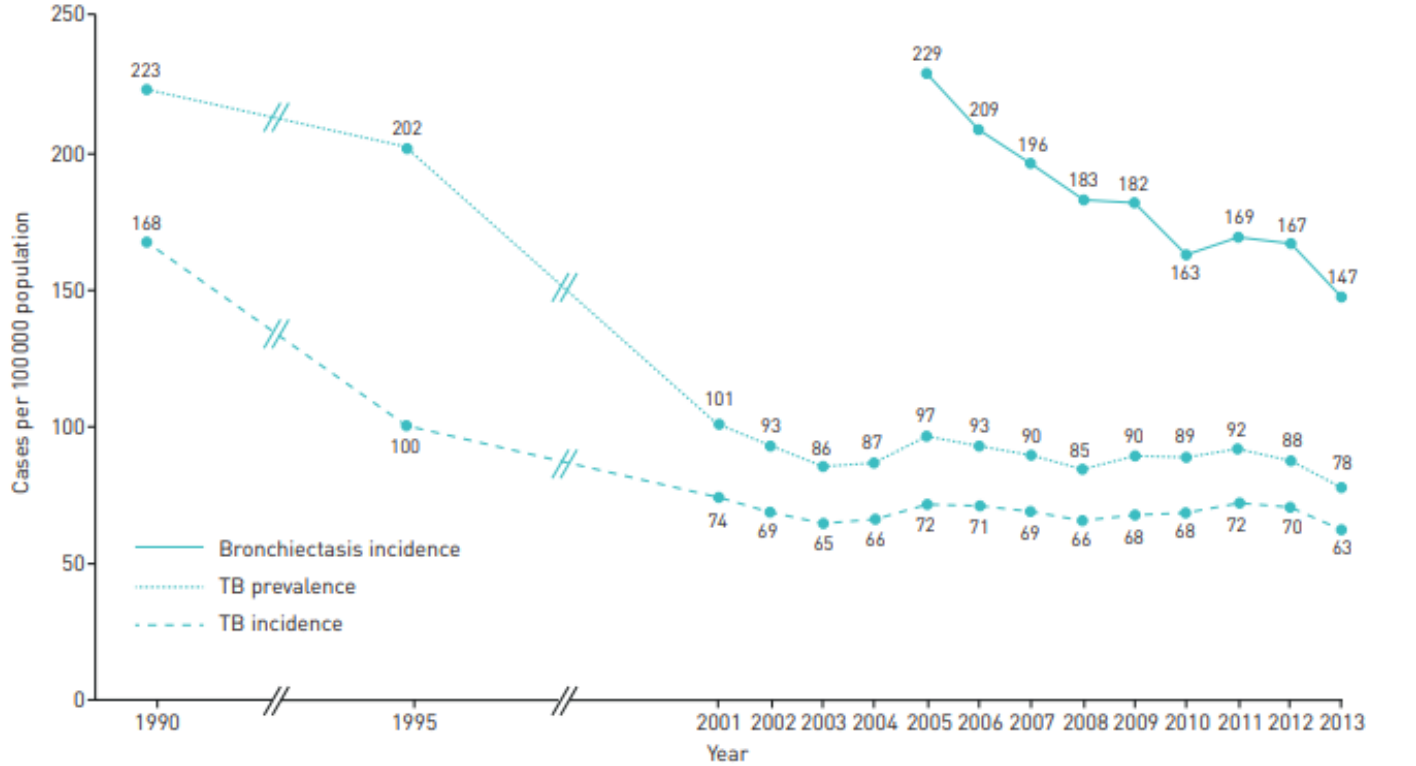


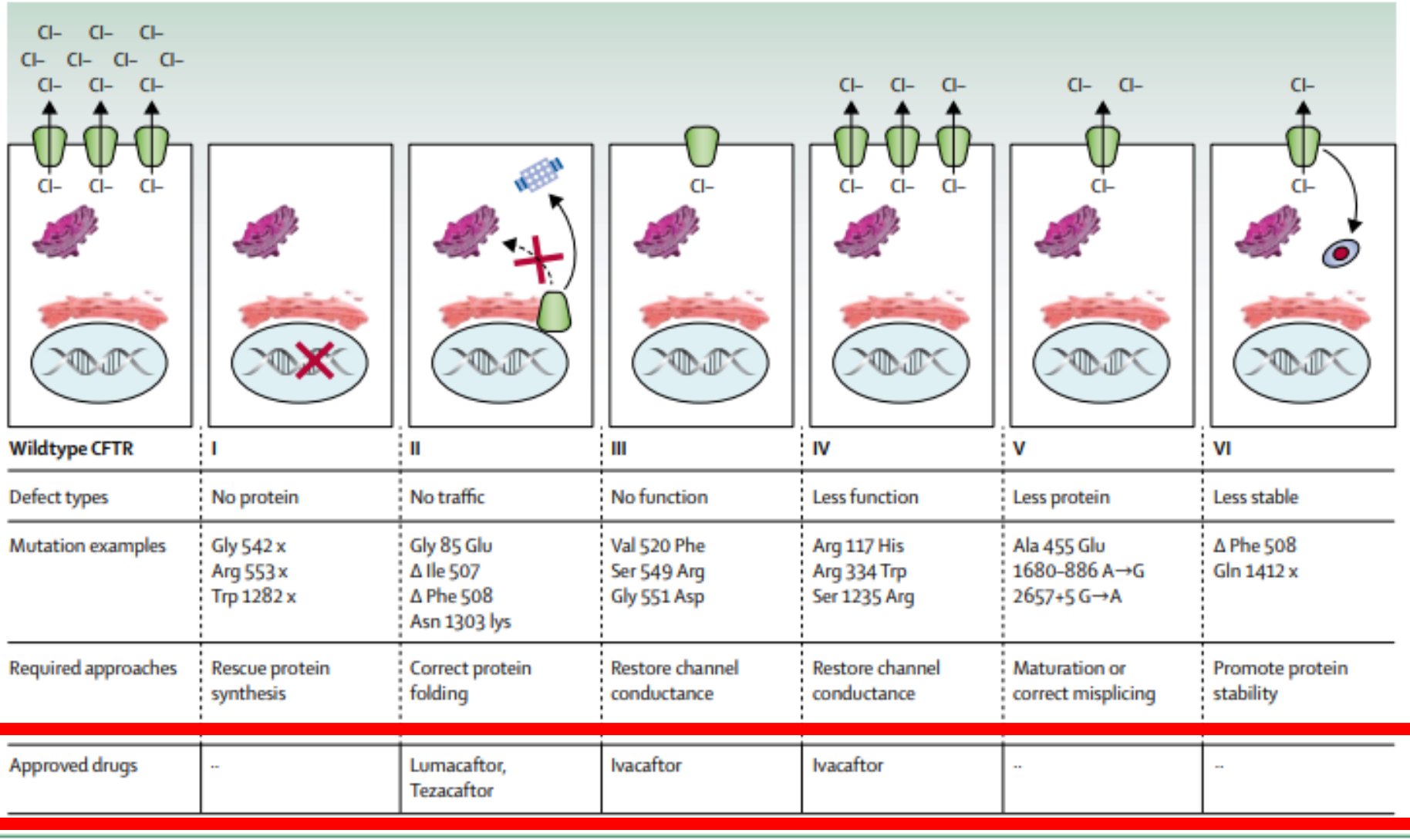
FIGURE 1 Incidence of bronchiectasis, prevalence of tuberculosis (TB), and incidence of TB in South Korea. TB prevalence and incidence data in 1990 and 1995 were not age-adjusted.

Causes of Bronchiectasis

Cause	Details or associated conditions
Post-infectious damage	Tuberculosis, whooping cough, non-tuberculous mycobacteria
Mechanical obstruction	Intrinsic (tumour or foreign body), extrinsic (lymph node)
Congenital	Defective bronchial wall, pulmonary sequestration
Inflammatory pneumonitis	Aspiration of gastric contents, inhalation of toxic gases
Excessive immune response	Allergic bronchopulmonary aspergillosis, lung transplant rejection, chronic graft versus host disease
Abnormal mucous clearance	Primary ciliary dyskinesia, cystic fibrosis, Young's syndrome
Fibrosis	Cryptogenic fibrosing alveolitis, sarcoidosis
Diffuse panbronchiolitis	Predominantly seen in Japanese patients
Deficient immune response	Hypogammaglobulinaemia, human immunodeficiency
Infertility	Cystic fibrosis, Young's syndrome, primary ciliary dyskinesia
Inflammatory bowel disease	Ulcerative colitis, Crohn's disease, coeliac disease
Connective tissue disease	Rheumatoid arthritis, systemic lupus erythematosus
Malignancy	Acute or chronic lymphatic leukaemia
Yellow nail syndrome	Discoloured nails, lymphoedema, pleural effusions
α1 antiproteinase deficiency	More commonly causes emphysema
Mercury poisoning	May cause Young's syndrome

BMJ 2007;335:1089-93

Cystic Fibrosis



	Wildtype CFTR	I	II	III	IV	V	VI
Defect types		No protein	No traffic	No function	Less function	Less protein	Less stable
Mutation examples		Gly 542 x Arg 553 x Trp 1282 x	Gly 85 Glu Δ Ile 507 Δ Phe 508 Asn 1303 lys	Val 520 Phe Ser 549 Arg Gly 551 Asp	Arg 117 His Arg 334 Trp Ser 1235 Arg	Ala 455 Glu 1680–886 A→G 2657+5 G→A	Δ Phe 508 Gln 1412 x
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation or correct misplicing	Promote protein stability
Approved drugs		--	Lumacaftor, Tezacaftor	Ivacaftor	Ivacaftor	--	--

Figure 2: **CFTR mutation classification**

Lancet 2018; 392: 880-890

반복적인 가래 기침을 주소로 내원한 9세 여아에서 발견된 낭성섬유증 1례: CFTR 유전자 변이 D339Y, Q220X

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=Abstract=

A case Report of a Classic Cystic fibrosis Pediatric Patient in Korea Carrying Very Rare CFTR Gene Mutations (D993Y and Q220X)

Min Jung Kim, M.D., Jung Wan Kang, M.D., Ji Hyun Lee, Ph.D.*, Kyung Won Kim, M.D., Myung Hyun Sohn, M.D., Min Goo Lee, M.D.*, Myung-Joon Kim, M.D.†, and Kyu-Earn Kim, M.D.

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Cystic fibrosis is the most common autosomal recessive disease in Caucasian. Cystic fibrosis is caused by cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations that lead to dysfunction of chloride ion channel regulations in the epithelium. Cystic fibrosis can affect multiple organ functions, resulting in various signs and symptoms. Typically, chronic airway infection, maldigestion, failure to thrive, and male infertility can occur. There are approximately 1800 CFTR gene mutations which have been identified thus far. However, there are only a few types of mutations reported in Korea because the prevalence of the disease is different among ethnicitiess and nations. Despite its rarity, reports of CFTR mutations or diagnosed patients on the rise. Therefore, we have to detect better outcomes as early as possible based on a precise understanding of the disease entity. We report a 9-year-old girl carrying D339Y and Q220X gene mutations, as the first case report of a D339Y mutation in Korea. **[Pediatr Allergy Respir Dis(Korea) 2011;21:61-66]**

Key Words : Cystic fibrosis, CFTR gene mutation, Korea

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- 9년 8개월 여아
- 4년 전부터 반복되는 기침, 가래
- PHx
  - 생후 3일부터 반복되는 구토,
  - 생후 10일 경 태변흡입증후군으로 인한 장폐색으로 수술
  - 생후 1개월에 패혈증
  - 생후 3개월 폐렴으로 vent (+) ICU care
  - 생후 5개월 폐렴으로 입원시 hyponatremia, hypochloremia
  - 6, 7세 경에도 폐렴으로 입원
  - 타병원에서 4세경부터 recurrent wheezing 으로 inhaler 시작한 상태
- 가족 유전자 검사상 부모 양쪽으로부터 각각 CFTR 변이 유전되었음 확인

Multicenter Surveillance of Cystic Fibrosis in Korean Children

Hyung Young Kim,[1] **Soo-Jong Hong**,[2] **Kangmo Ahn**,[3] **Dong In Suh**,[4] **Shin Hye Noh**,[5] **Soo Yeon Kim**,[6] **Jinho Yu**,[2] **Jung Min Ko**,[4] **Min Goo Lee**,[5] **Kyung Won Kim**[6*]

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Allergy Asthma Immunol Res 2022;14(5):494-504

Table 1. Participant characteristics at diagnosis and follow-up (n = 18)

Clinical features	Value
Age (yr) at diagnosis	9.2 (0.4, 19.2)
Male	7 (38.9)
Growth retardation at diagnosis	
Weight < 3 percentile	11 (61.1)
Height < 3 percentile	7 (38.9)
Respiratory failure at diagnosis	6 (33.3)
Follow-up period (yr)	3.7 (0.4, 14.3)
Deaths*	4 (22.2)
Age (yr) at death	10.6 (5.8, 16.8)
Survival period (yr)	4.2 (0.4, 6.9)

Data are presented as number (%) and median (minimum, maximum).
*The causes of death were pneumonia (n = 1), septic shock (n = 1), rejection after lung transplantation (n = 1), and liver failure/cerebral hemorrhage (n = 1).

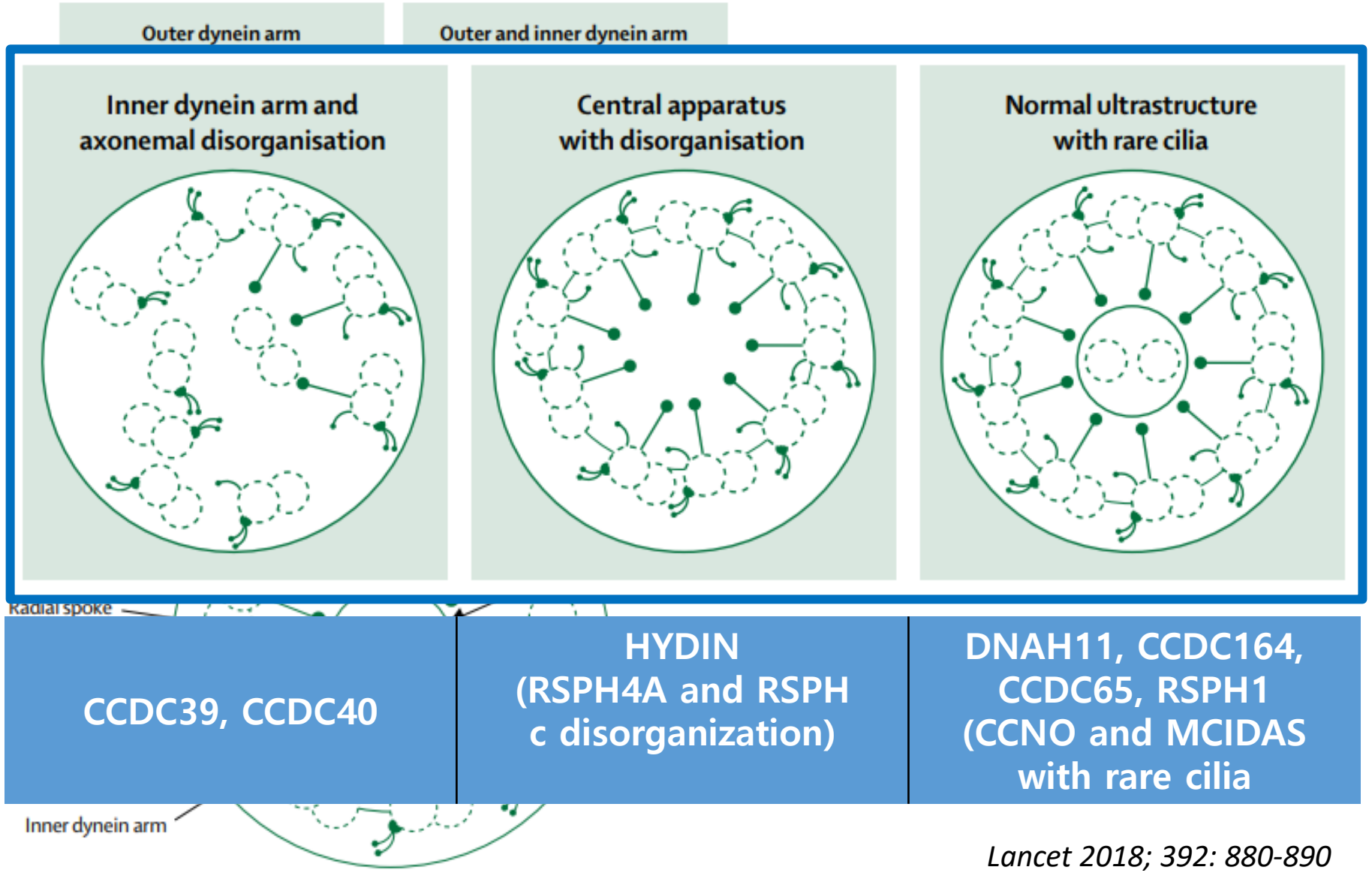
Table 2. Clinical and laboratory findings at diagnosis (n = 18)

Clinical and laboratory findings at diagnosis	Value
Findings applied for the diagnostic criteria	
Typical clinical features	
Respiratory tract	18 (100.0)
Digestive tract	15 (83.3)
Others*	3 (16.7)
A history of CF in a sibling (n = 15)	4 (26.7)
Sweat chloride concentration ≥ 60 mmol/L (n = 8)†	7 (87.5)
Two mutations known to cause CF on separate alleles‡	16 (88.9)
Respiratory findings at diagnosis	
Chest CT	
Bronchiectasis	14 (77.8)
Cyst formation	1 (5.6)
Spirometry (n = 10)	
FEV1 *z* score	−3.61 (−5.78, 1.78)
FEV1/FVC *z* score	−3.38 (−4.40, −0.60)
FEF25–75 *z* score	−4.45 (−5.78, 0.54)
Sputum culture (n = 15)	
Pseudomonas aeruginosa	10 (66.7)
Staphylococcus aureus	6 (40.0)
Others§	6 (40.0)

Table 3. Results of *CFTR* gene testing and the sweat chloride test in 18 Korean patients with CF

Patient No.	Age at diagnosis	Sex	First variant		Second variant		Sweat test (mmol/L)
			cDNA name	Protein name	cDNA name	Protein name	
1*	14 yr 11 mon	Female	**Exon 16-17b deletion**	-	**Exon 16-17b deletion**	-	ND
2	9 yr 2 mon	Male	**Exon 16-17b deletion**	-	**Exon 16-17b deletion**	-	103.7
3*	6 yr 3 mon	Male	**Exon 16-17b deletion**	-	Exon 14a deletion	-	ND
4a*	14 yr 1 mon	Male	**Exon 16-17b deletion**	-	c.3871C>T	p.Gln1291Ter	ND
5a*	19 yr 3 mon	Male	**Exon 16-17b deletion**	-	c.3871C>T	p.Gln1291Ter	ND
6*	9 yr 2 mon	Male	**Exon 16-17b deletion**	-	**c.3196C>T**	p.Arg1066Cys	ND
7	5 yr 8 mon	Male	**Exon 16-17b deletion**	-	**c.1657C>T**	p.Arg553Ter	ND
8	13 yr 8 mon	Female	**Exon 16-17b deletion**	-	c.2052del	p.Lys684fs	ND
9b	7 yr 11 mon	Female	c.1322T>C	p.Leu441Pro	c.223C>T	p.Arg75Ter	123
10b	9 yr 4 mon	Female	c.1322T>C	p.Leu441Pro	c.223C>T	p.Arg75Ter	Fail
11	7 mon	Female	c.1322T>C	p.Leu441Pro	c.273+2T>A	-	ND
12*	5 yr	Female	c.1322T>C	p.Leu441Pro	-	-	88.7
13	9 yr 8 mon	Female	**c.2977G>T**	p.Asp993Tyr	**c.658C>T**	p.Gln220Ter	71.1
14	13 yr 3 mon	Female	**c.2977G>T**	p.Asp993Tyr	**c.263T>G**	p.Leu88Ter	ND
15*	5 yr 11 mon	Female	c.2562T>G	p.Thr854 =	c.2562T>G	p.Thr854 =	97.5
16*	4 mon	Male	**c.263T>G**	p.Leu88Ter	c.2089_2090insA	p.Arg697LysfsX33	ND
17*	10 mon	Female	**c.3908dupA**	p.Asn1303fs	**c.1766+2T>C**	-	102
18*	13 yr 9 mon	Female	c.3871C>T	p.Gln1291Ter	IVS8-5T	p.Met470Val	108.1

Primary Ciliary Dyskinesia



CCDC39, CCDC40	HYDIN (RSPH4A and RSPH c disorganization)	DNAH11, CCDC164, CCDC65, RSPH1 (CCNO and MCIDAS with rare cilia

Lancet 2018; 392: 880-890

PCD gene associated with situs inversus

PCD without situs inversus

Structural defect of ODA

Heavy chain

*DNAH5**

*DNAH11**

Intermediate chains

DNAI1

DNAI2

Light chain

DNAL1

NME8

Docking defect of ODA

ODA Docking Complex

ARMC4

CCDC103, CCDC114

CCDC151

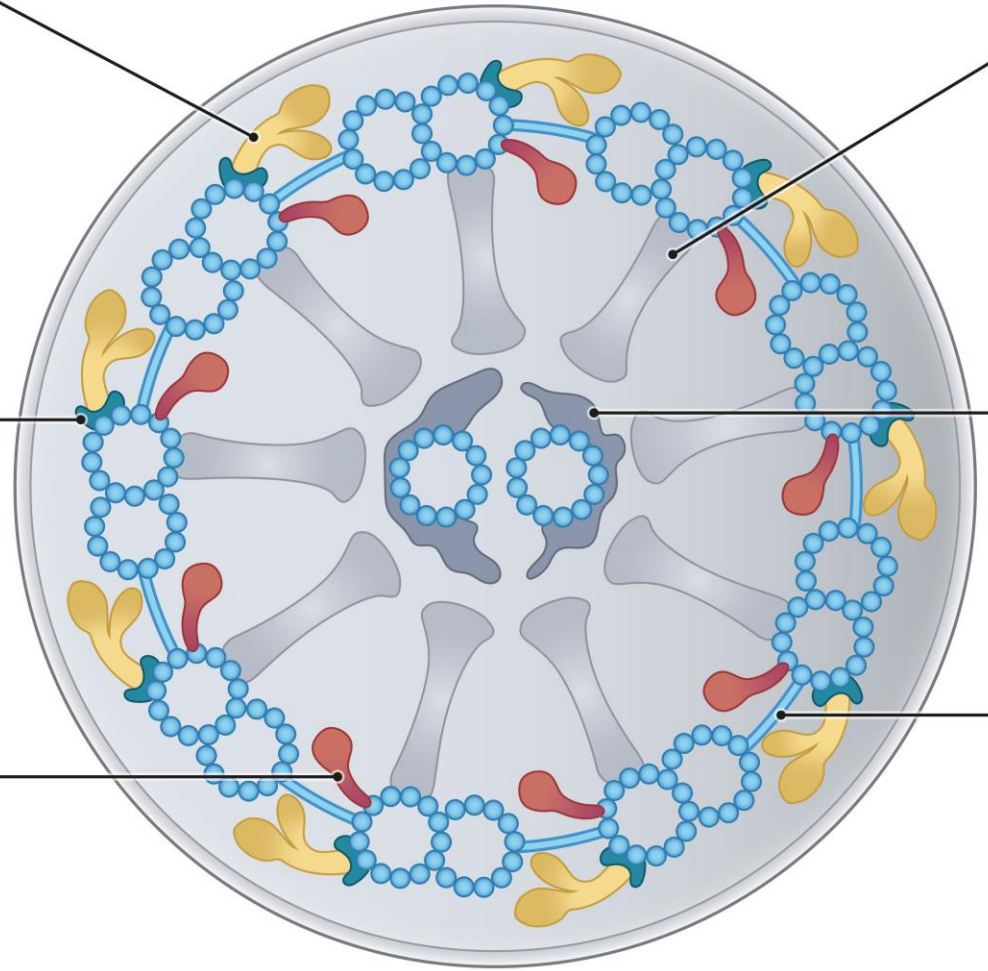
MNS1

TTC25

96 nm axonemal ruler

*CCDC39**

CCDC40



Defect of radial spoke

RSPH1

RSPH3

RSPH4A

RSPH9

DNAJB13

Defect of central pair protein

HYDIN

STK36

Isolated nexin link defects

CCDC65

CCDC164 (DRC1)*

GAS8

Reduced Motile cilia number

*MCIDAS**

CCNO

Defects in cytoplasmic preassembly of DA

DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5 LRRC6, ZMYND10, SPAG1, C21ORF59, DNAAF6, CFAP300

Subtle or no respiratory disease

MNS1, DNAH9

Oh JY, Kim KW et al. In revised.

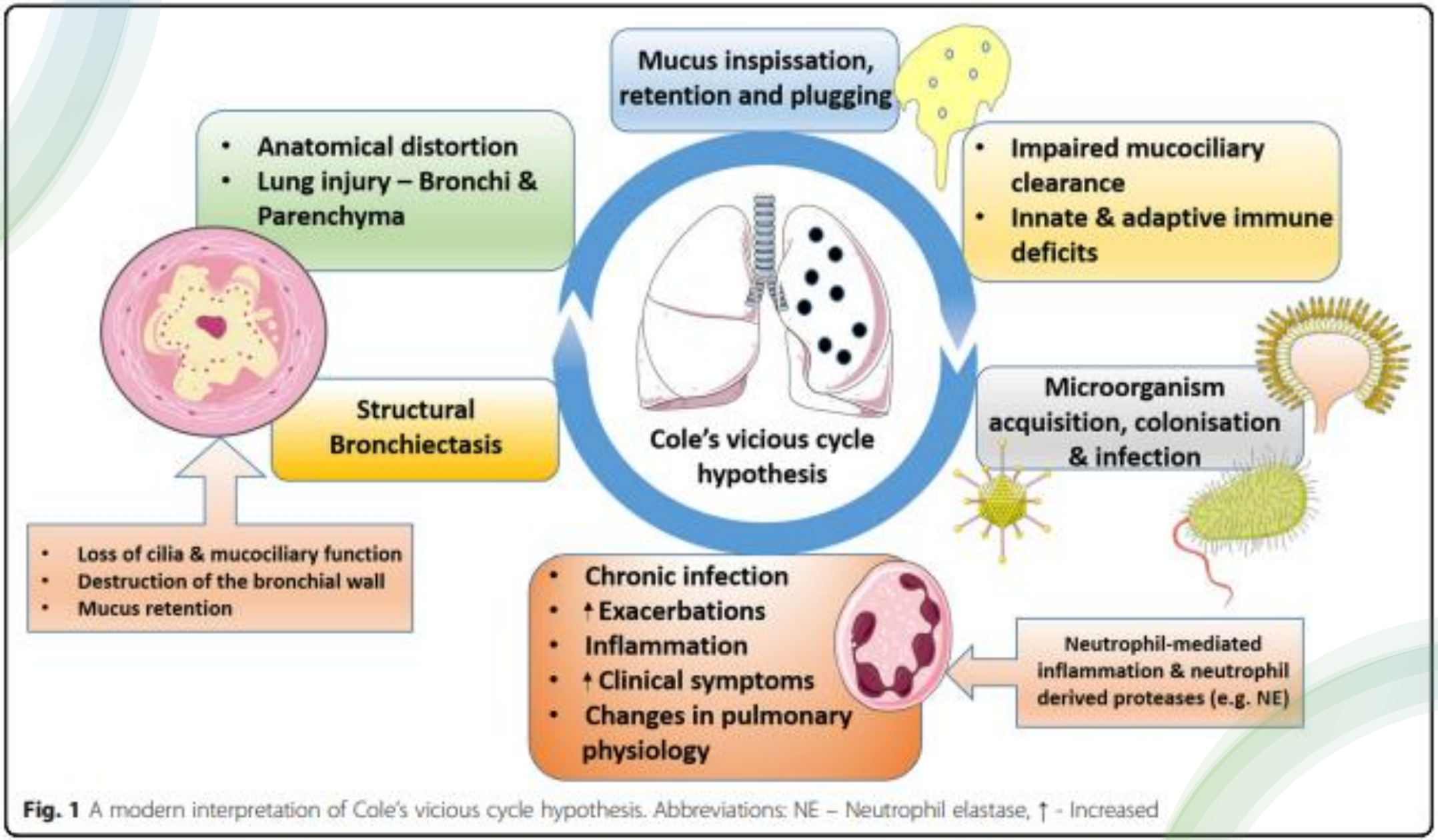


Fig. 1 A modern interpretation of Cole's vicious cycle hypothesis. Abbreviations: NE – Neutrophil elastase, ↑ - Increased

BMC Pulm Med 2018;18:83

	Age of onset	Radiology	Microbiology	Symptoms or features	Physiology or lung function
Idiopathic	Women who are post-menopausal at any age	Any radiological pattern	*Pseudomonas aeruginosa*, *Haemophilus influenzae*, any pathogens or none	Any	Any
Post-infective bronchiectasis	Any	Any pattern, unilobular	Any pathogens or none	Should typically have onset of symptoms soon after a severe infection	Any
Connective tissue disease	Any	Any	Any	Poor prognosis or rapidly progressive, features of systematic disease[54]	Airflow obstruction (but other patterns seen)
Immune deficiency	Primary immune deficiency often at young age, secondary immune deficiency at any age	Lower lobe	Any	Frequent exacerbations, pneumonia, non-respiratory infections	Airflow obstruction
Allergic bronchopulmonary aspergillosis	Any	Central bronchiectasis, infiltrates	Typically *Staphylococcus aureus*[55]	Thick sputum, wheeze, recurrent exacerbations, background of asthma	Airflow obstruction
Non-tuberculous mycobacteria	Women who are post-menopausal at any age	Middle lobe and lingula bronchiectasis, tree in bud, nodular changes	In addition to non-tuberculous mycobacteria, can have typical bacteria such as *P aeruginosa*	Dry bronchiectasis, chronic cough, malaise, weight loss, systemic features, low body-mass index, scoliosis, pectus excavatum	Any
Primary ciliary dyskinesia	Usually presents in childhood	Middle or lower lobes	*H influenzae*, any	Chronic rhinosinusitis, recurrent otitis media	Any
Chronic obstructive pulmonary disease	Smokers or ex-smokers older than 40 years	Lower lobe cylindrical bronchiectasis	Any or no bacterial infection	Recurrent exacerbations, sputum production	Airflow obstruction (bronchiectasis more common with more severe airflow obstruction)[56]
Inflammatory bowel disease	Any	Any lobes affected, bronchiolitis, could include other features of inflammatory bowel disease-associated lung disease	Often no pathogens isolated	Gross bronchorrhea, which is often responsive to corticosteroids	Airflow obstruction
Cystic fibrosis	Young age of onset but can present in adulthood	Upper lobes	*P aeruginosa*, *S aureus*, others	Rhinosinusitis, infertility, pancreatitis, malabsorption, gastrointestinal symptoms	Airflow obstruction

Lancet 2018; 392: 880–90

Pediatric BE

- c-HRCT protocols (without MDCT scans) have insufficient sensitivity to detect early signs of bronchiectasis in some children.
- **a lower bronchoarterial ratio should be used in children**
- - the normal ratio is around 0.5 (aged <5 years), and in older children (<18 years), the upper limit is less than 0.8.

Pediatr Allergy Immunol 2021;32:647-57
J Allergy Clin Immunol 2022;149:867-73

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In Children

	Proportion of cohort with symptom (%)		Odds ratio* (95% CI)
	High-income countries from non-Indigenous settings	Low-income countries	
Chronic wet or productive cough	35	28–100	527 (45·4–6102)†
Wet cough not resolved after 4 weeks	..	..	7·5 (0·3–161·5)
Recurrent protracted bacterial bronchitis	..	..	18·4 (1·0–349·7)†
Recurrent pneumonia	..	46	22·8 (1·2–424·3)†
Previous pneumonia	4–47	23–100	Not examined
Haemoptysis	0	5–41	Absent in cohort
Wheeze or reversible airway obstruction	10–40	20–66	Absent in cohort
Chest pain	3	3–43	Absent in cohort
Dyspnoea or exertional dyspnoea	1	9–81	4·3 (0·2–109·7)
Faltering growth	4	10–66	Absent in cohort
Feeding difficulties	..	..	22·8 (1·2–424·3)†
Digital clubbing	..	4–73	7·5 (0·3–161·5)
Chest deformity	..	15–29	4·3 (0·2–109·7)
Differential airway sounds (on chest auscultation)	..	..	7·5 (0·3–161·5)
Crackles	..	47	10·8 (0·5–218·9)
Abnormal chest radiograph	..	..	41·6 (2·3–750)†
Median forced expiratory volume in 1 s (% predicted)	71–95	52–80	4·3 (0·2–109·7)
Median forced vital capacity (% predicted)	77–96	58–82	..

Prevalence of symptoms & signs related to bronchiectasis

Table 1 Main presenting symptoms of bronchiectasis in adults

Symptoms at presentation[6,7]
Cough (90.2–96%)
Sputum (75%)
Excessive sputum volume (mean ± SD: 38 ± 34 mL)
Haemoptysis (26–51.2%)
Dyspnoea (60%)
Chest pain (19–46.3%)
Recurrent chest infections (mean ± SD: 2.4 ± 1.6/year)

Respirology 2019;24(5):413-422

Lancet 2018; 392: 866–79

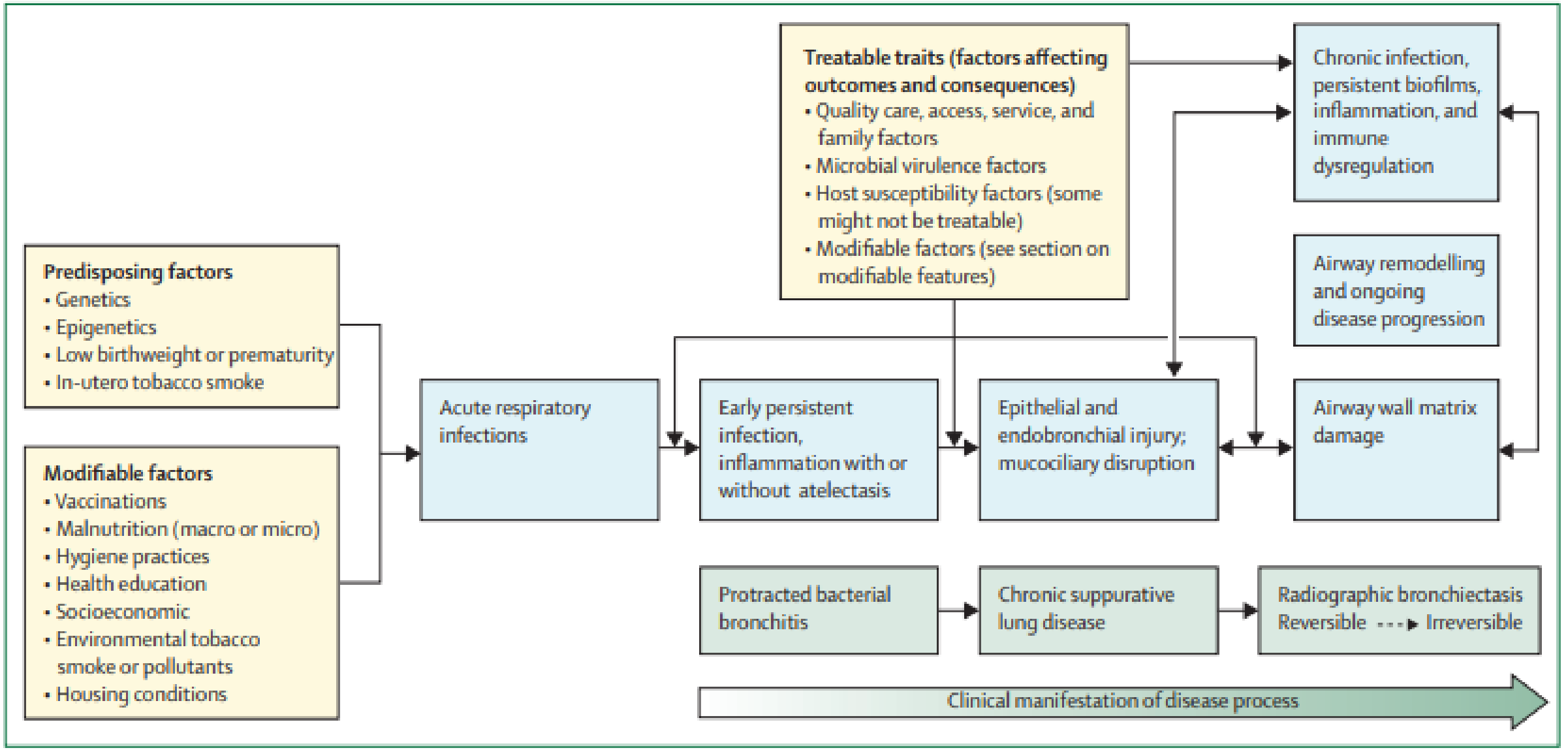
Study	Nikolaizik et al. [25] N = 41	Edwards et al. [55] N = 60	Singleton et al. [56] N = 46	Chang et al. [52] N = 65	Santamaria et al. [57] N = 105	Kapur et al. [58] 2012 N = 113	Brower et al. [59] 2014 N = 989 [a]
Setting n (%)	City, England	City, New Zealand	Remote, Indigenous, Alaska	Remote, Indigenous, Australia	City, Italy	City, Australia	Mixed locations
Postinfectious (severe pneumonia)	12 (29)	15 (15)	42 (92)	58 (90)	7 (6.7)	14 (12)	174 (19)
Tuberculosis	0	0	2 (4)	1 (1)	0	0	Not described
Inherited immune deficiency	8 (20)	7 (12)	0	2 (3)	11 (10.5)	13 (12)	158 (17)
Primary ciliary dyskinesia	7 (17)	0	0	0	25 (23.8)	2 (2)	66 (7)
Congenital malformations	6 (15)	1 (1)	0	1 (1)	0	0	34 (4)
Secondary immune defects	3 (7)	0	0	0	0	5 (4)	29 (3)
Aspiration of exogenous toxicants or foreign body	2 (5)	1 (2)	1 (2)	0	0	2 (2)	Combined with below
Aspiration or GERD	0	6 (10)	1 (2)	3 (5)	4 (3.8)	12 (11)	91 (10)
CF-like or CF	1 (2)	0	0	0	0	0	0
Interstitial lung disease including bronchiolitis obliterans	0	0	0	0	0	3 (3)	12 (1)
"Asthma"	0	0	0	0	0	0	Not described
Others	0	0	0	0	0	0	18 (2)

Kendig's disorders of the respiratory tract in children 9th Ed

Pediatric BE

- **Making an early diagnosis** in managing & preventing complications
- abnormally increased airway dilatation **- maybe reversible**
- early diagnosis with appropriate investigations can identify treatable underlying causes (ex. Primary immunodeficiency)
- early diagnosis with optimal management will improve the patient's and their family's QoL, reduce on-going pulmonary damage.

Pediatr Pulmonol 2023;58:2183–2186
Respirology 2019;24(5):413-422



Framework for the development of paediatric bronchiectasis

Lancet 2018; 392: 866–79

Protracted Bacterial Bronchitis (PBB)

- **Persistent bacterial bronchitis**
- A condition that is likely a precursor, **pre-bronchiectasis state**
- Airway infection using conventional bacterial culture, with neutrophilia on bronchoalveolar lavage (BAL) (or induced sputum)
- **Without significant airway dilatation**

Kendig's disorders of the respiratory tract in children 9th Ed
Respirology 2019:24;1053-1062

Protracted Bacterial Bronchitis (PBB)

- **Chronic productive cough, daily for > 4weeks**
- **mostly in preschool children**
- H.influenzae(m/c), M.catarrhalis, S.pneumoniae, S.aureus
- P.auruginosa, S.aureus in CF patients
- Adenovirus – m/c viral isolate
- Associated with airway malacia

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Respirology 2019:24;1053-1062

TABLE 1—Diagnostic Criteria for Protracted Bacterial Bronchitis

1. Original microbiologic-based case definition[8](also termed PBB-micro)
   i. Presence of chronic wet cough (>4 weeks)
   ii. Lower airway infection (recognized respiratory bacterial pathogens growing in sputum or at BAL at density of a single bacterial specifies $\geq 10^4$ colony-forming units/ml)
   iii. Cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate)
2. Modified clinical-based case definition[45] (also termed PBB-clinical)
   i. Presence of chronic wet cough (>4 weeks)
   ii. Absence of symptoms or signs of other causes of wet or productive cough[1]
   iii. Cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate)
3. PBB-extended = PBB-clinical or PBB-micro, but cough resolves only after 4 weeks of antibiotics
4. Recurrent PBB = recurrent episodes (>3 per year) of PBB

[1]Specific cough pointers[45,94,95] are: chest pain, history suggestive of inhaled foreign body, dyspnea, exertional dyspnea, hemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sino-pulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis, signs of respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles, chest radiographic changes (other than perihilar changes), lung function abnormalities].

Pediatr Pulmonol 2016;51:225-242

Outcomes of PBB in children

Table 2 Univariable and multivariable analyses of risk factors for BE in PBB

	BE present	BE absent	Univariable analysis		Multivariable analysis*	
	n = 16, n (%)	*n* = 150, n (%)	OR (95% CI)	*P*-value	$OR_{adjusted}$ (95%CI)	*P*-value
Sex, Male	11 (69)	105 (70)	0.94 (0.31-2.87)	0.92		
Recurrent PBB Yr one	14 (88)	74 (49)	7.19 (1.58-32.73)	**0.011**	9.6 (1.8-50.1)	**0.008**
≥ 2 siblings	9 (56)	46 (31)	2.91 (1.02-8.28)	**0.046**	2.9 (0.9-10.0)	0.09
Childcare attendance	12 (86)[a]	100 (82)[b]	1.27 (0.26-6.10)	0.77		
Smoke exposure	4 (25)	47 (31)	0.73 (0.22-2.38)	0.60		
Asthma	7 (44)	38 (25)	2.2 (0.80-6.58)	0.12	3.3 (0.92-12.1)	0.07
Tracheomalacia	7 (44)	67 (45)	1.0 (0.34-2.72)	0.94		
Bronchomalacia	4 (25)	47 (31)	0.73 (0.22-2.38)	0.60		
BAL neutrophilia (>20%)	9 (56)	74 (52)[c]	1.20 (0.42-3.40)	0.73		
BAL eosinophil (>1.5%)	3 (19)	10 (7)[c]	3.23 (0.79-13.23)	0.10	4.8 (0.8-28.5)	0.09
BAL pathogen						
Adenovirus PCR	2 (13)	23 (16)[c]	0.8 (0.16-3.50)	0.71		
S. aureus	3 (19)	11 (7)	2.92 (0.72-11.80)	0.13	2.3 (0.4-12.7)	0.34
H. influenzae	12 (75)	56 (37)	5.04 (1.55-16.37)	**0.007**	5.1 (1.4-19.1)	**0.013**
M. catarrhalis	7 (43)	36 (24)	2.46 (0.86-7.08)	0.094	2.7 (0.8-9.4)	0.13
S. pneumoniae	3 (19)	34 (23)	0.78 (0.21-2.92)	0.72		

*factors included in the model are listed in this column. PBB, protracted bacterial bronchitis; BE, bronchiectasis; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction. Incomplete data available for highlighted variables [a]n = 14, [b]n = 122, [c]*n* = 143. Boldface denotes statistical significance $p < 0.05$

Total 194 children
Median f/u duration – 59mon

- ongoing symptoms – 67.5%
- Bronchiectasis – 9.6%
- Asthma at final – 27.1%

(allergen sIgE (+) at baseline, bronchomalacia)

Respirology 2021;26:241–248

Chronic Suppurative Lung Disease (CSLD)

- a clinical syndrome where symptoms of chronic endobronchial suppuration exist **without c-HRCT evidence of bronchiectasis**
- Whether bronchiectasis and CSLD are different clinical entities or simply reflect a spectrum of airway disease remains undetermined.
- Both are chronic suppurative airway diseases and respond to similar treatment regimens.

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BE vs CSLD

- Thus, we recommend that HRCT scans are best performed in a nonacute state and bronchiectasis be diagnosed if symptoms of CSLD are present when HRCT findings meet the pediatric rather than adult radiological criteria.

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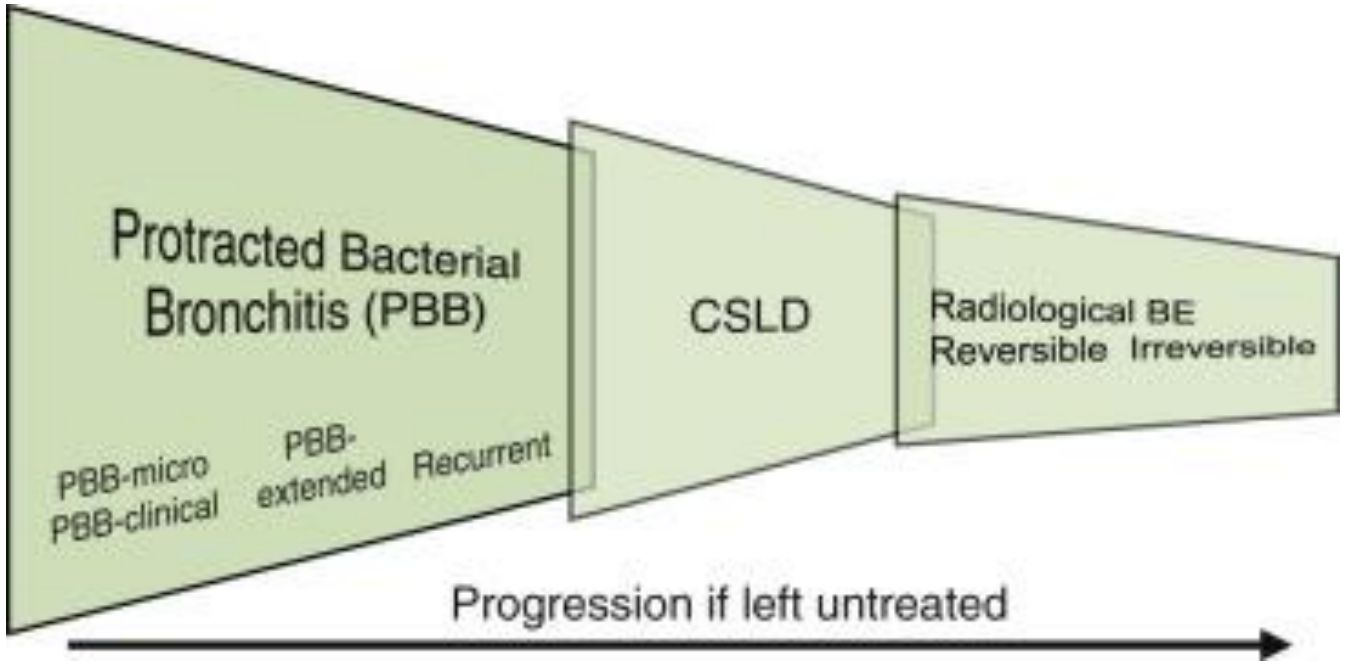
Interrelationship between PBB, CSLD, and BE



Pediatr Pulmonol 2016;51:225-242

European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis

Eur Respir J 2021; 58: 2002990

In children/adolescents suspected of bronchiectasis…

- High-resolution MDCT scans with HRCT be used instead of conventional HRCT to diagnose bronchiectasis in children/adolescents.
  (Conditional recommendation, very low quality of evidence.)

- Paediatric-derived BAR (defined by the ratio of the inner diameter of the airway to the outer diameter of the adjacent artery) of >0.8 is used to define abnormality instead of the adult cut-off of >1–1.5. *(Conditional recommendation, very low quality of evidence stemming from the narrative review.)*

Asthma-based Medications

- Not using ICS with or without LABA routinely in either the short- or long-term, irrespective of stability or exacerbation. *(Conditional recommendation, very low quality of evidence.)*

- ICS maybe beneficial in those with eosinophilic airway inflammation.
- In the absence of any studies on the use with SABA in bronchiectasis, we cannot make any recommendation.
- For some, SABA may be beneficial as pre-airway clearance therapies.

Mucoactive agents

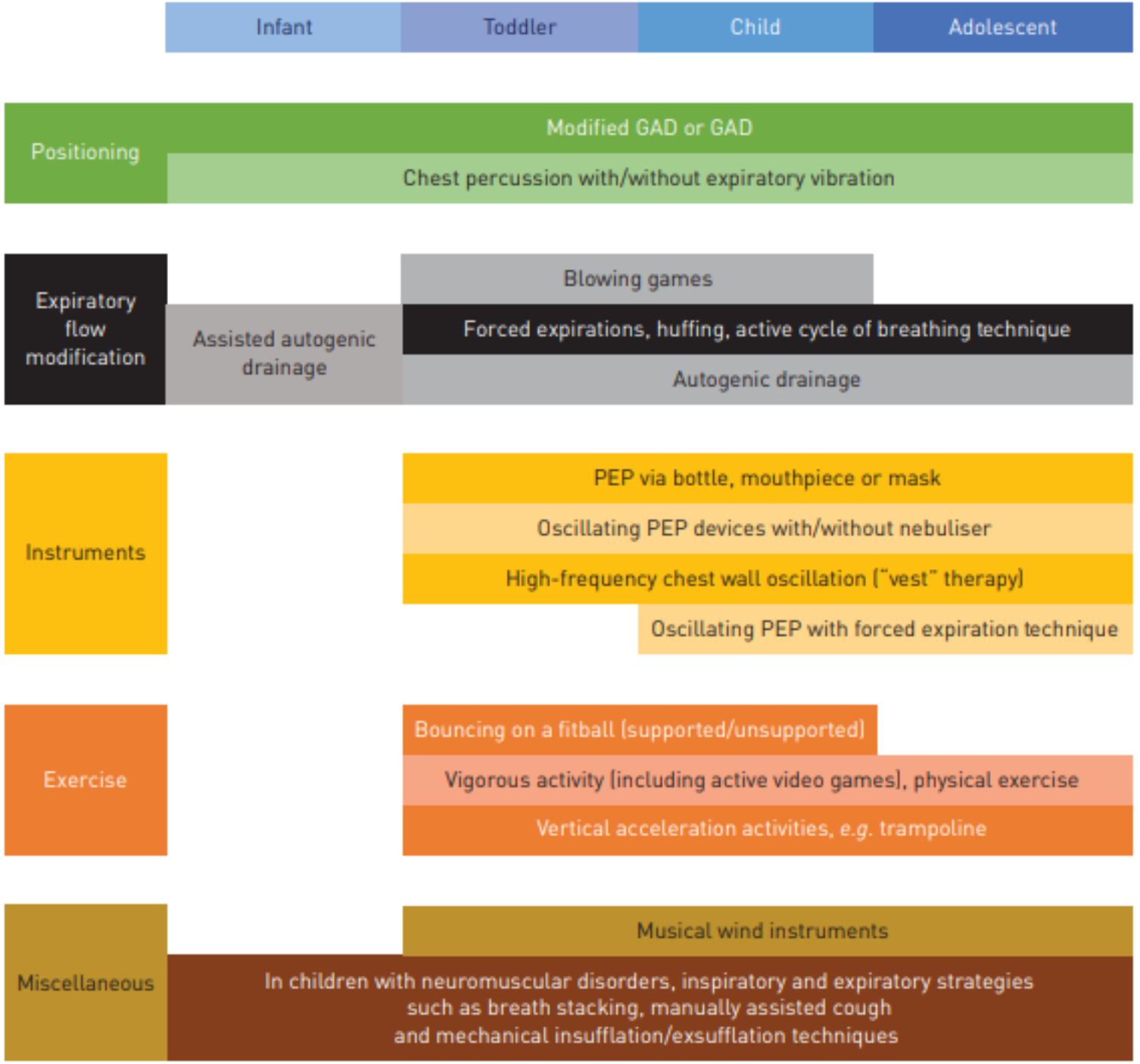
- Recombinant human DNase (rhDNase) is not used routinely. *(Strong recommendation, very low quality of evidence.)*
- Bromhexine is not used routinely. *(Conditional recommendation, very low quality of evidence.)*
- Neither inhaled mannitol nor hypertonic saline are used routinely. *(Conditional recommendation, very low quality of evidence.)*
  - Inhaled mannitol or 6–7% hypertonic saline may be considered in selected patients.

Airway Clearance

- In children/adolescents with bronchiectasis, we recommend they are taught and receive regular ACT or manoeuvres. *(Strong recommendation, low quality of evidence.)*

- The frequency of ACT is best individualised.
- As children/adolescents mature, techniques may need to be changed, and thus the ACT type and frequency is best reviewed at least biannually by physiotherapists with expertise in paediatric respiratory care.
- During acute exacerbations of bronchiectasis, children/adolescents should receive ACT more frequently.

Development- and Age-appropriate Individualized ACT



Use of Antibiotics

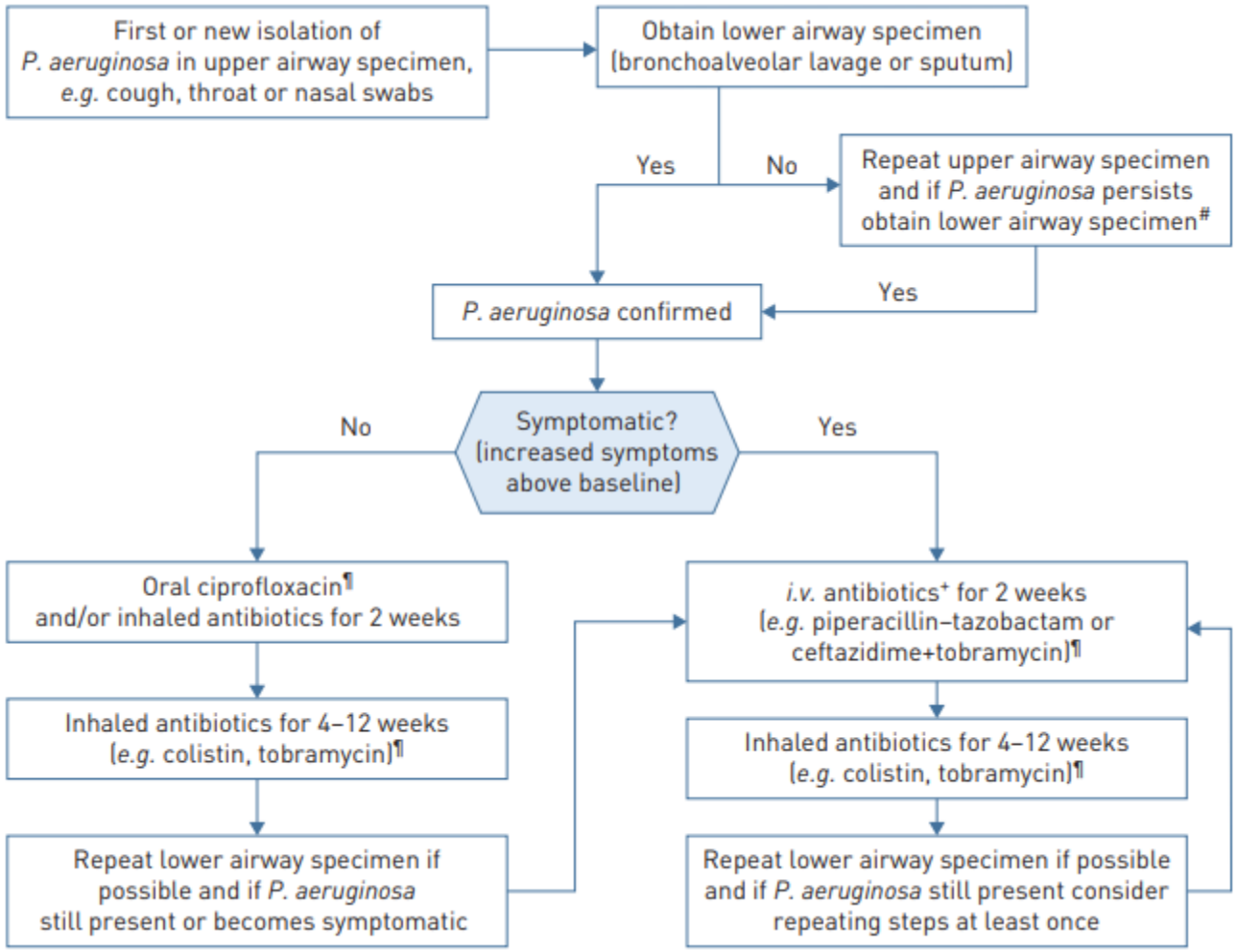
- With bronchiectasis and an acute respiratory exacerbation, a systemic course of an appropriate antibiotic is used for 14 days. *(Strong recommendation, moderate quality of evidence.)*

- The empiric antibiotic of choice - amoxicillin-clavulanate,
- Depending on patient's airway cultures, and Hx of anti hypersensitivity reaction
- When the exacerbation is severe (e.g. the child/adolescent is hypoxic) and/or when the child/adolescent does not respond to oral antibiotics, intravenous antibiotics will be needed.

Eradication treatment, irrespective of Sx ?

We suggest eradication therapy following an initial or new detection of P. aeruginosa.

(Conditional recommendation for the intervention, very low quality of evidence.)



Long-term macrolide

- In children/adolescents and adolescents with bronchiectasis and recurrent exacerbations, we recommend treatment with long-term macrolide antibiotics to reduce exacerbations. *(Strong recommendation, low quality of evidence.)*

- Only in those who have had more than one hospitalised or three or more non-hospitalised exacerbations in the previous 12 months.
- With regular assessment for at least 6 months
- Children/adolescents receiving longer treatment courses (>24 months) should continue to be evaluated for risk versus benefit.

핵심질문	권고문	근거수준	권고 등급
1. 소아청소년 기관지확장증 악화 예방에 마크롤라이드 장기 치료가 효과적인가요?	18세 이하 소아청소년 기관지확장증 환자에서 악화 예방 및 증상 경감을 위한 마크롤라이드 장기 치료를 권고한다. 단, 마크롤라이드 장기 치료에 따른 마크롤라이드 내성 폐렴사슬알균(*S. pneumoniae*) 및 포도상구균(*S. aureus*) 출현 가능성이 높다. 치료에 따른 악화 예방 및 증상 경감 이득과 마크롤라이드 내성 균주 감염으로 인한 위해를 고려하여 사용할 것을 권고한다.	moderate	B
2. 소아청소년 기관지확장증 급성 악화에 대한 항생제 적정 사용 기간은?	18세 이하 소아청소년 기관지확장증 환자에서 기관지확장증의 급성악화에 대한 항생제 적정 사용 기간을 특정할 근거가 불충분하다.	low	I
3. 소아청소년 기관지확장증 악화에 대한 치료로 항생제 흡입 치료가 효과적인가요?	18세 이하 소아청소년의 기관지확장증 환자에서 항생제 흡입치료 사용을 권고할 근거가 불충분하다.	low	I
4. 소아청소년 기관지확장증 악화 예방에 진해거담제 치료가 효과적인가요?	18세 이하 소아청소년 기관지확장증 악화 예방에 진해거담제(경구, 흡입) 사용을 권고할 근거가 불충분하다.	very low	I

5. 소아청소년 기관지확장증 악화 예방에 흡입 스테로이드제 치료가 효과적인가요?	18세 이하 소아청소년 기관지확장증 환자에서 악화 예방에 흡입 스테로이드제 사용을 권고할 근거가 불충분하다.	very low	I
6. 소아청소년 기관지확장증 악화 예방에 비스테로이드소염제(경구 또는 흡입) 치료가 효과적인가요?	18세 이하 소아청소년 기관지확장증 환자에서 악화 예방에 비스테로이드소염제(경구, 흡입) 사용을 권고할 근거가 불충분하다.	very low	I
7. 소아청소년 기관지확장증 악화 예방과 폐기능 향상에 고장성 식염수 흡입 치료가 효과적인가요?	18세 이하 소아청소년 기관지확장증 환자에서 폐기능 향상과 급성악화 예방을 위하여 고장성 식염수 흡입 치료를 권고한다. 그러나 영아의 폐기능 향상에 대해서는 사용을 권고할 근거가 불충분하다.	moderate	B
8. 소아청소년 기관지확장증 악화 예방에 대안적 호흡물리요법은 전통적 호흡재활요법 대비 효과적인가요?	18세 이하 소아청소년 기관지확장증 환자에서 폐기능 개선을 위해 전통적 호흡재활보다 대안적 호흡물리요법 등을 권고할 근거가 불충분하다.	low	I

In Summary

- The global incidence and prevalence of pediatric BE unrelated to CF ↑
- Early diagnosis is a key objective in managing bronchiectasis.
- CF, primary immune deficiency, or PCD should be considered in children.
- Underlying lung diseases and auto-immune disorders are more common in adults.
- The need for personalized treatment to improve lung function, prevent exacerbation, and improve QoL

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With the Love of God, Free Humankind from Disease and Suffering

Thank you for your attention !!