Comorbid chronic rhinosinusitis is associated with increased health care utilization in patients with asthma and bronchiectasis

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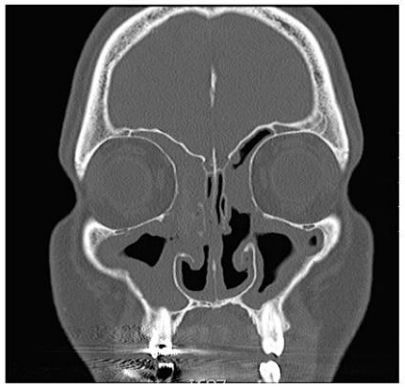
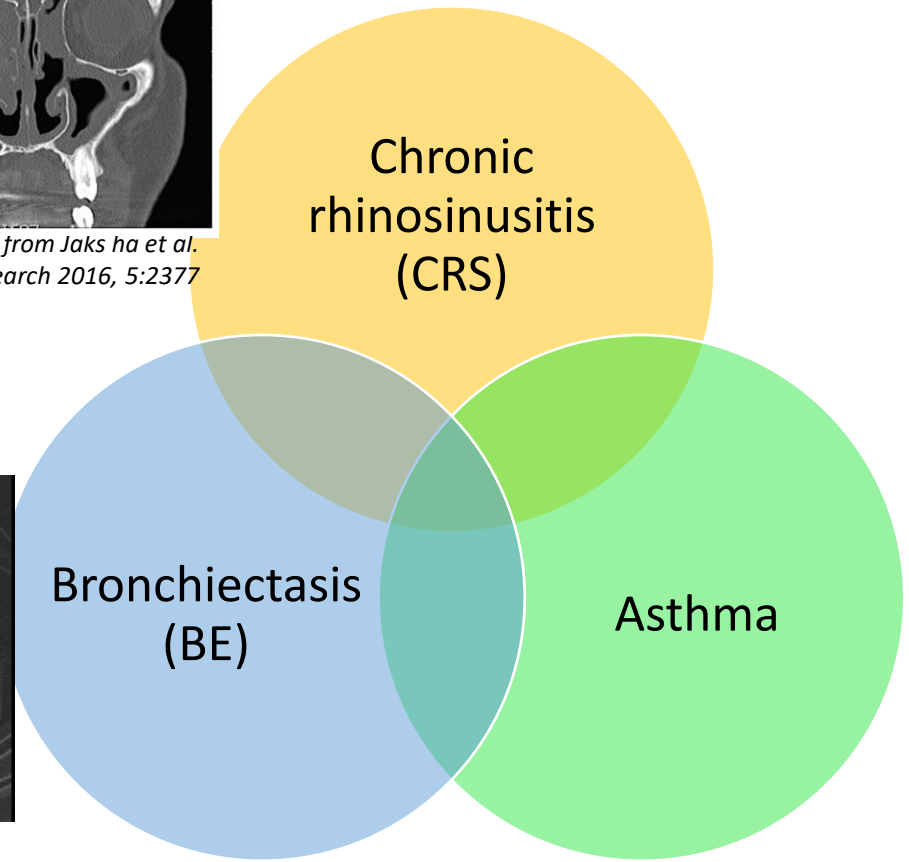
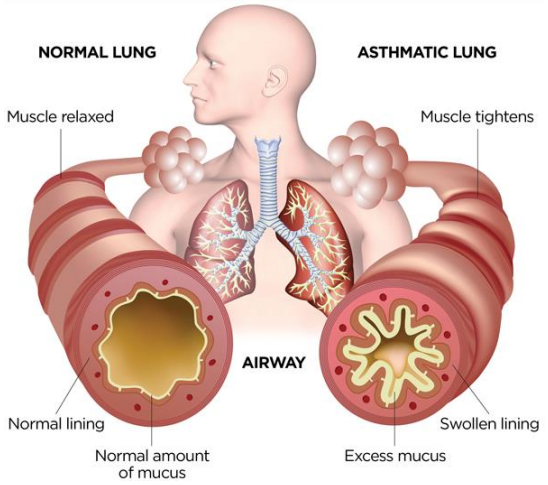
Asthma, bronchiectasis and CRS…



Images from Jaks ha et al. F1000Research 2016, 5:2377

Image from Martina Contarini et al. Eur Respir Rev 2018;27:180016





Normal vs asthma lung. Image from AAFA.org Access Dec 12 2021

Bronchiectasis (BE)

- Characterized permanent dilation of airway
- Presents with chronic cough and productive sputum

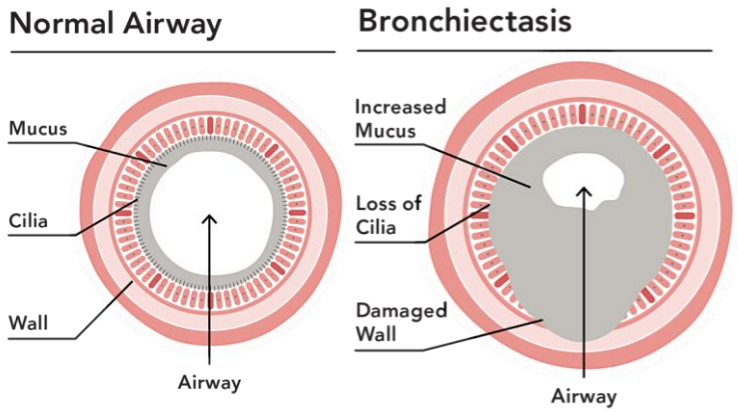


Image from https://smartvest.com

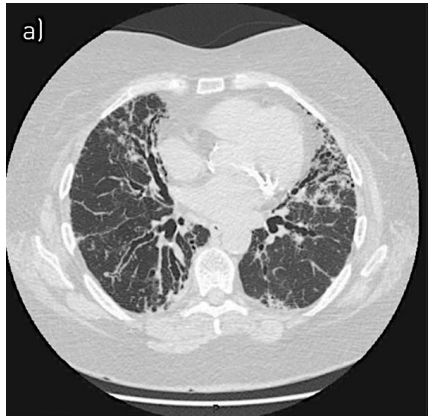


Image from Martina Contarini et al. Eur Respir Rev 2018;27:180016

- Diagnosis made by HR CT
- Diameter of bronchi > diameter of adjacent pulmonary artery

- Associated with vicious cycle of recurrent infection, airway inflammation, and structural damage

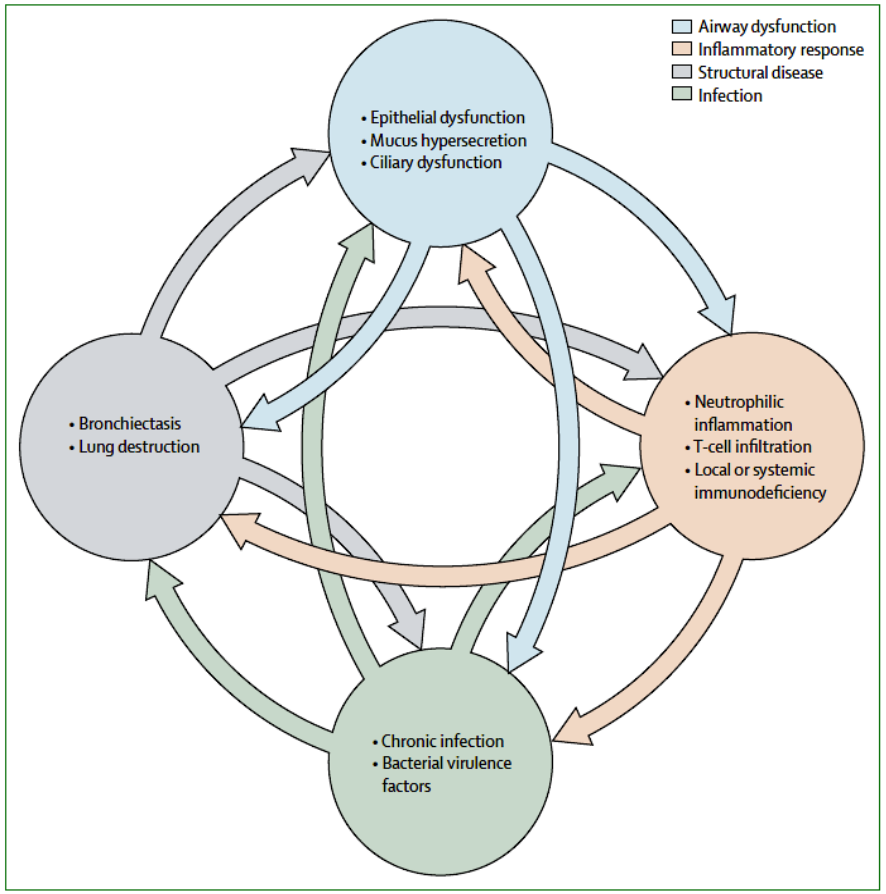


Image from Fume et al. Lancet 2018; 392: 880–90

BE is a heterogenous condition from diverse etiologies

- Cystic fibrosis, primary ciliary dyskinesia
- Non-cystic fibrosis bronchiectasis
  - Immune deficiencies
  - Autoinflammatory disorders (e.g. IBD) and CTD
  - Chronic airway inflammatory disorders (e.g. COPD, asthma, ABPA)
  - Chronic infections (e.g. NTB)
  - Idiopathic

In US Bronchiectasis Research Registry, asthma was comorbid in 29% (515/1783) of patient with BE
(Aksamit et al CHEST 2017; 151(5):982-992)

Table 2
Etiology of non-CF Bronchiectasis.

Characteristics	Pasteur [24] (2000)	Shoemark [25] (2007)	Lonni [26] (2015)	Olveira [27] (2017)	Visser [28] (2019)
n	150	165	1258	2047	566
Age	52.7 ± 15.2	49 ± 16	67	64.9 ± 18.4	71
Female (%)	62.7	42	60	55	71
Idiopathic	80 (53%)	43 (26%)	502 (40%)	496 (24%)	184 (32.5%)
Post-infectious	44 (29%)	52 (32%)	257 (20%)	613 (30%)	159 (28%)
Immunodeficiency	12 (8%)	11 (7%)	73 (5.8)	192 (9.4)	21 (3.7%)
ABPA	11 (7%)	13 (8%)	56 (4.5%)	18 (0.9%)	22 (3.9%)
PCD (genetic)	3 (1.5%)	17 (10%)	21 (1.7%)	60 (2.9%)	22 (3.9%)
CTD/Rheumatoid arthritis	4 (3%)	3 (2%)	128 (10%)	29 (1.4%)	8 (1.4%)
Young syndrome	5 (3%)	5 (3%)		5 (0.2%)	
Aspiration/GERD	6 (4%)	2 (1%)	8 (0.6%)	33 (1.5%)	14 (2.5%)
Yellow Nail syndrome			1 (0.1%)	4 (0.2%)	
NTM infection		2 (1%)		233 (11.4%)	48 (8.5%)
Cystic Fibrosis (genetic)	4 (3%)	2 (1%)		255 (12.5%)	
IBD/Ulcerative colitis	2 (<1%)	5 (3%)	24 (1.9%)	5 (0.2%)	
Pan bronchiolitis	1 (<1%)	4 (2%)		2 (0.1%)	
Congenital malformation	1 (<1%)		7 (0.6%)	14 (0.7%)	
COPD			129 (15%)	160 (7.8%)	19 (3.4%)
Asthma			41 (3.3%)	110 (5.4%)	21 (3.7%)
Alpha-1-antitrypsin deficiency			8 (0.6%)	10 (0.5%)	

J.S. Imam et al. Respiratory Medicine 166 (2020) 105940

BE is prevalent in severe asthma

- In a cohort of 398 nonsmokers with uncontrolled moderate-to-severe asthma, 28.4% had bronchiectasis; the prevalence was higher (33.6%) in patients with severe asthma *(Padilla-Gallo et al. Respir Res 2018).*
- In a cohort of 184 severe asthma, 47% had bronchiectasis on CT *(Coman et al, Ann Allergy Asthma Immuno 2018).*

Author	Year	*n*	Severity of asthma	Prevalence of BX	Notes
Kim [11]	2018	91	Severe[a]	35.2%	–
Weatherburn [16]	2017	84 505	Not described	0.8%	Cross-sectional analysis of routine primary care electronic medical records for 1424 378 adults in the United Kingdom, 84 505 with asthma. In nonasthmatics ($n = 1339\,873$) prevalence of bronchiectasis of 0.2%
Henkle [8]	2017	511/1247	Not described	19/28	Two different sources: NTM Info & Research Patient Survey (E-mail survey, 511 responders)/Bronchiectasis and NTM Research Registry
Dimakou [13]	2017	40	Severe[b]	67.5%	–
Kang [7]	2014	2270	Not described	2.2%	–
Lujan [17]	2013	100	Not described	12.0%	Patients divided in SDA and NSDA. Prevalence of BX: 20% in SDA group and 4% in NSDA group
Menzies [18]	2011	133	Severe[c]	35.3%	–
Bisaccioni [19]	2009	245	Not described	26.8%	–
Gupta [10]	2009	463	Severe[d]	40.0%	
Oguzulgen [14]	2007	1680	All/non specified	3.0%	Asthma was severe in 49% of patients with BX versus 31% of pure asthmatics
Paganin [20]	1996	126	All/non specified	80.0%	–

(Perez-Miranda et al. Current Opinion in Pulm Medicine 2019).

Bronchiectasis is associated with worse outcome in asthma

- Bronchiectasis is independently associated with increased risk of hospitalization in severe asthma and had higher blood eosinophils *(Coman et al, Ann Allergy Asthma Immuno 2018).*
- Patients with bronchiectasis had a lower FEV1% and FEV1/FVC and more infectious exacerbations compared to patients without bronchiectasis. The eosinophilic asthma phenotype showed highest prevalence of bronchiectasis *(Bendien et al, Respiration 2019)*
- Patients with bronchiectasis had worse asthma control, worse quality of life, lower FEV1 and increased rate of asthma exacerbation. *(Malipiero et al. Expert Rev Respir Med 2021)*

Bronchiectasis is characterized by neutrophilic inflammation *, but some are eosinophilic*

- High level of systemic IL-8 detected in patient with BE
- Elevated neutrophil elastase correlates BE exacerbation and severe disease (*Chamber et al. Am J Respir Crit Care Med 2017*)
- Subset of bronchiectasis patient (~30%) has eosinophilic inflammation; this subset of patient have lower FEV1, worse QoL, and more frequent exacerbation *(Oriano et al. Biomedicines 2021)*
- Case series of 12 patients with severe asthma+BE had reduced respiratory exacerbation after treatment with biologic targeting T2 inflammation. *(Kudlaty et al. Ann Allergy Asthma Immunol 2021)*

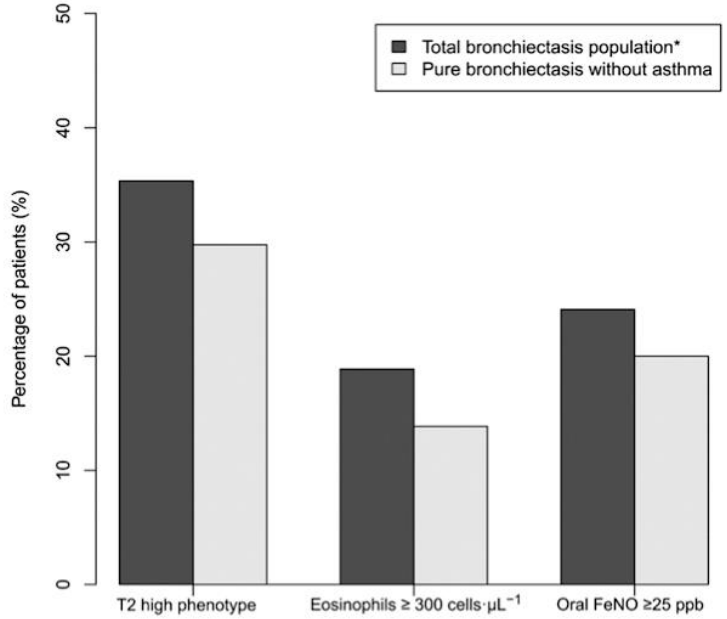
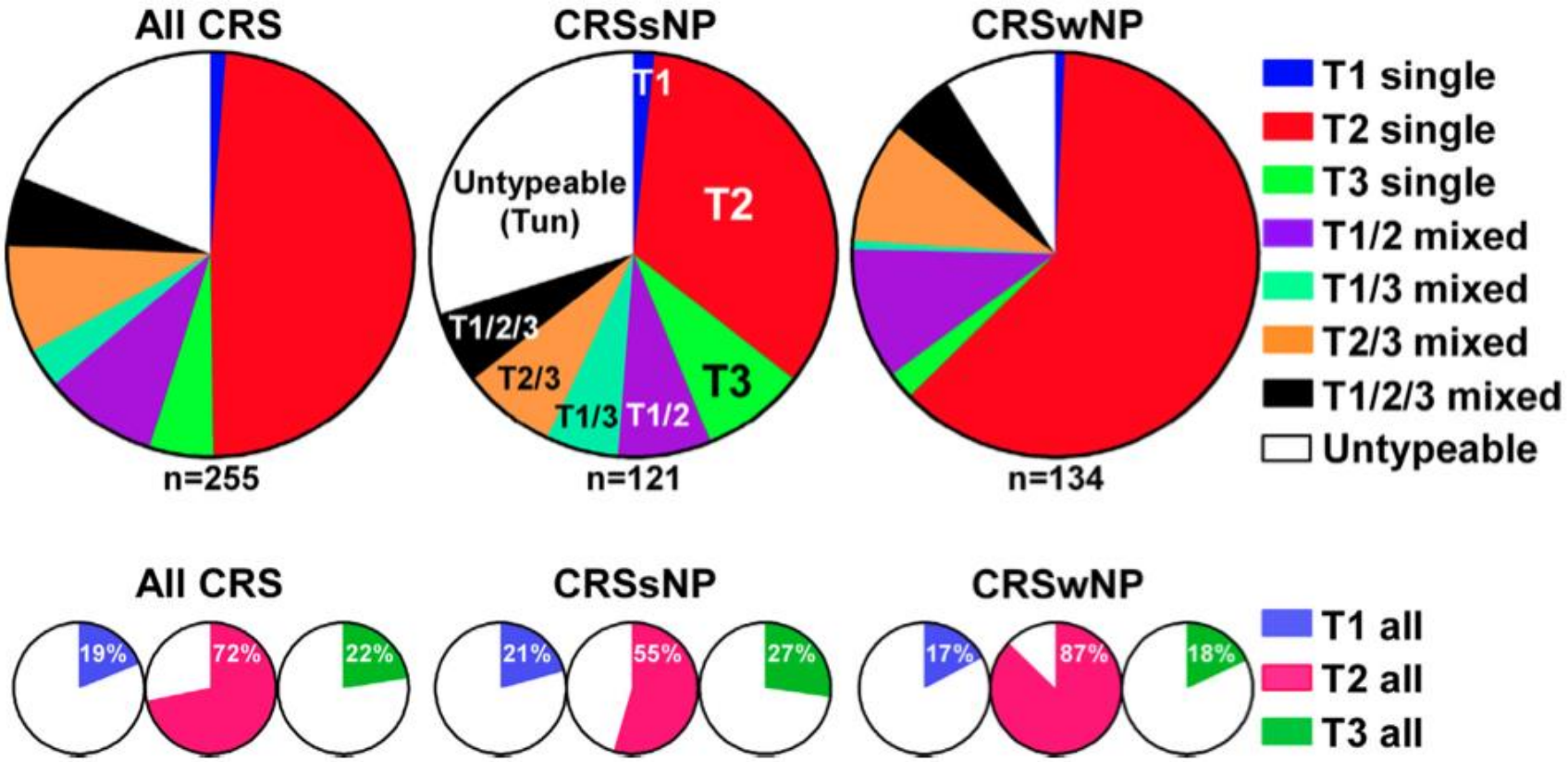


Figure 1. Prevalence of bronchiectasis patients with either T2 high endotype (either eosinophils ≥300 cells·μL^{-1} or oral FeNO ≥ 25 ppb) or eosinophils ≥300 cells·μL^{-1} or oral FeNO ≥ 25 ppb among the entire study population and those without asthma. * Including those with concomitant asthma.

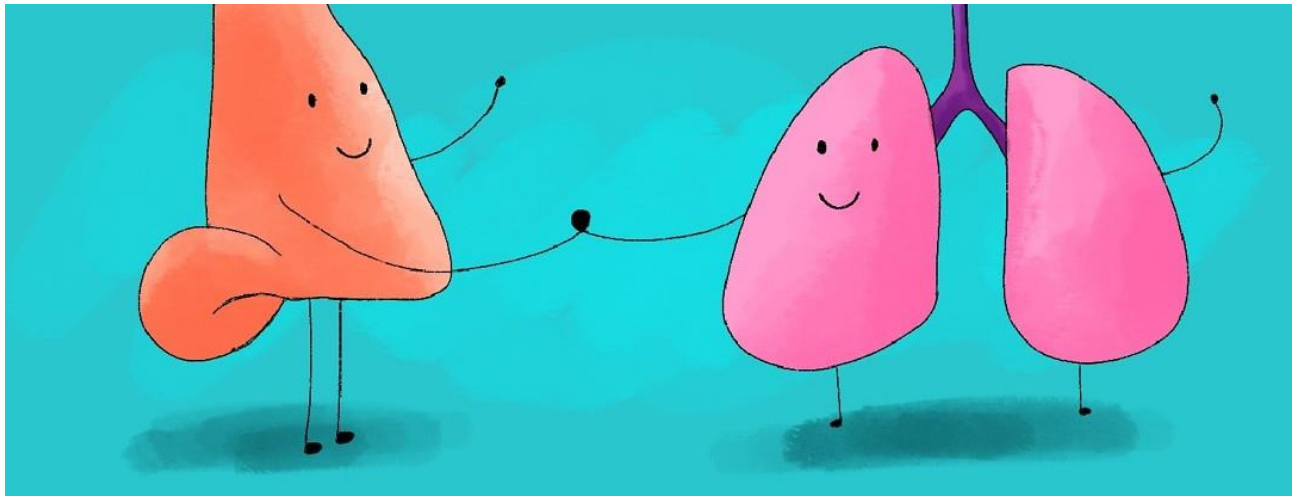
Oriano et al. Biomedicines 2021, 9, 772

Chronic Rhinosinusitis (CRS) predominantly T2 inflammation (*in western countries)



(Stevens et al. JACI in Practice 2019)

“Unified Airway Disease”

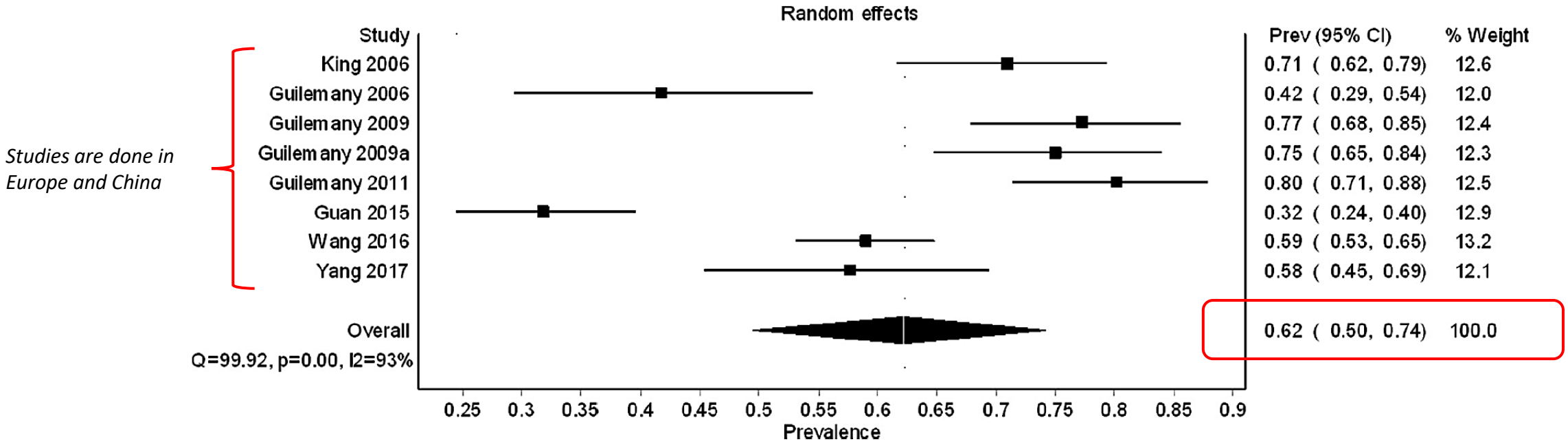


- Happy nose happy lung!
- High rate of coexistence of upper (CRS, AR) and lower airway disease (asthma)
- From a single inflammatory process

Image from Asthma.net Image URI: https://asthma.net/wp-content/uploads/2019/04/asthma-airways-14999-custom@2x-1080x412.jpg

Prevalence of CRS in bronchiectasis: meta-analysis

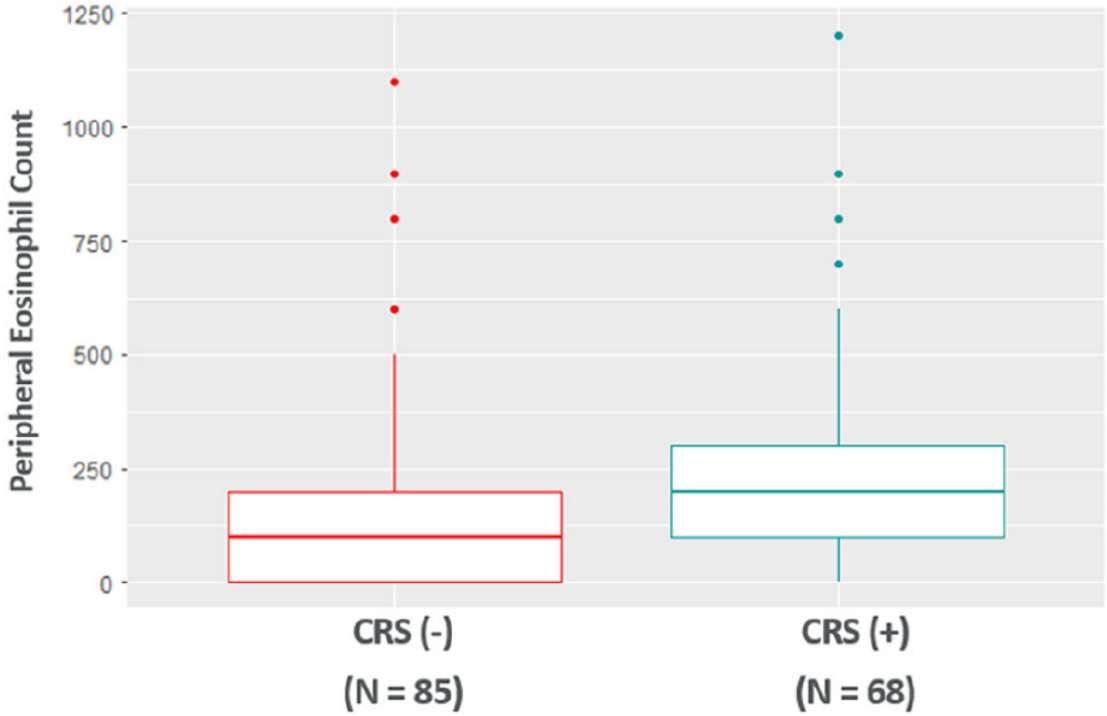
- CRS is present in **62%** of adults with bronchiectasis
- Associated with poorer health related QOL, greater degree of bronchiectasis disease severity, and more extensive radiographic diseases



Handley et al. J Allergy Clin Immunol Pract 2019;7:2004-12

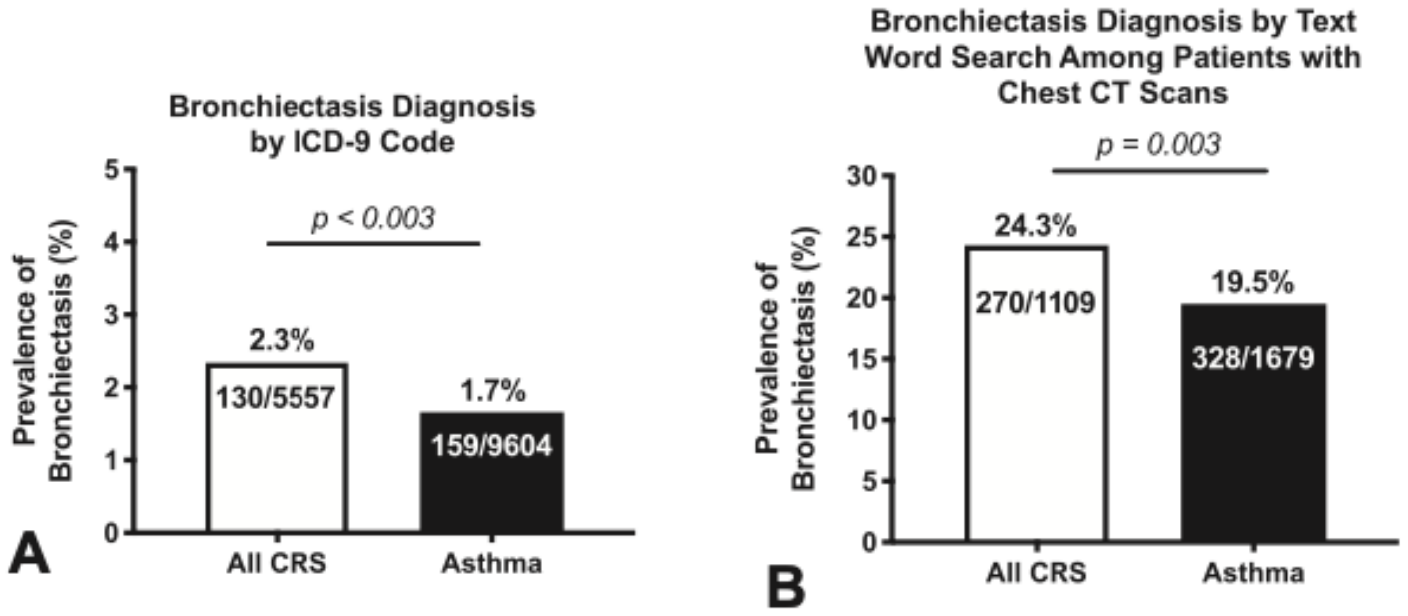
Prevalence of CRS in bronchiectasis: Northwestern

- CRS is present in **45%** of patients with bronchiectasis
- When comorbidities were adjusted, asthma ($p<0.02$), allergic rhinitis ($p<0.01$ GERD ($p<0.01$), and antibody deficiency ($p=0.01$) were independently associated with presence of CRS in bronchiectasis
- Peripheral eosinophil counts is higher in patients with CRS



Somani et al. Int Forum Allergy Rhinol. 2019;9: 1424–1429.

Bronchiectasis is more common in CRS than in asthma



(Peters et al. JACI in practice 2021).

Bronchiectasis is more common in CRSwNP vs CRSsNP

Table 1
Demographic and clinical characteristics of SANI population.

	All the patients (n = 695)	Patients with CRSwNP (n = 282)	Patients without CRSwNP (n = 413)	p values
Mean age, years	54.9 ± 16.6	54.9 ± 12.9	55.13 ± 13.7	0.836
Female, %	60.6	61.3	60.0	0.731
Mean age of asthma onset, years	33.7 ± 16.6	34.5 ± 15.9	33.0 ± 17.2	0.290
Atopy, %	75.9	72.6%	79.8	0.184
BMI (mean, Kg/m^2)	26.6 ± 16.7	27.1 ± 22.8	25.9 ± 4.8	0.390
Annual exacerbation rate, mean	3.03 ± 5.55	3.69 ± 7.43	2.46 ± 3.00	0.014
FEV_1% predicted, mean	73.6 ± 20.4	74.4 ± 19.3	73.0 ± 21.4	0.440
Prevalence of atopic dermatitis, %	5.9	8.6	3.4	0.019
Prevalence of bronchiectasis, %	15.5	20.9	11.9	0.001
Prevalence of GERD, %	26.9	27.5	24.6	0.572
FE_{NO} (mean, ppb)	44.3 ± 48.9	54.4 ± 53.8	34.6 ± 28.3	<0.0001
Blood eosinophils (mean, cells/mcl)	492.3 ± 612.5	513.6 ± 607.2	471.9 ± 618.2	0.466
Serum IgE (mean, kU/l)	459.2 ± 850.1	379.4 ± 394.7	533.3 ± 1114.1	0.058

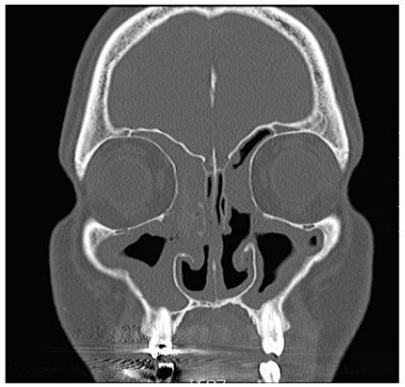
CRSwNP, chronic rhinosinusitis with nasal polyposis; BMI, body mass index; FE_{NO}: Fractional Exhaled Nitric Oxide; GERD: GastroEsophageal Reflux Disease.

(Canonica et al. Respiratory Medicine 166 (2020) 105947)

Impact of CRS on BE

- Not well studied and limited
- Sinus surgery did not improve lung function *(Wang et al. Acta Otolaryngo 2016 ;Kanjanaumporn Am J Rhinology&Allergy 2018)*
- Sinus surgery reduced frequency of exacerbation 6 months from surgery (*Wang et al. Acta Otolaryngo 2016)*
- Sinus surgery did not reduce frequency of antibiotic use for sinopulmonary infection 2 years post op *(Peters et al. JACI in practice 2021).*

Asthma, bronchiectasis and CRS…



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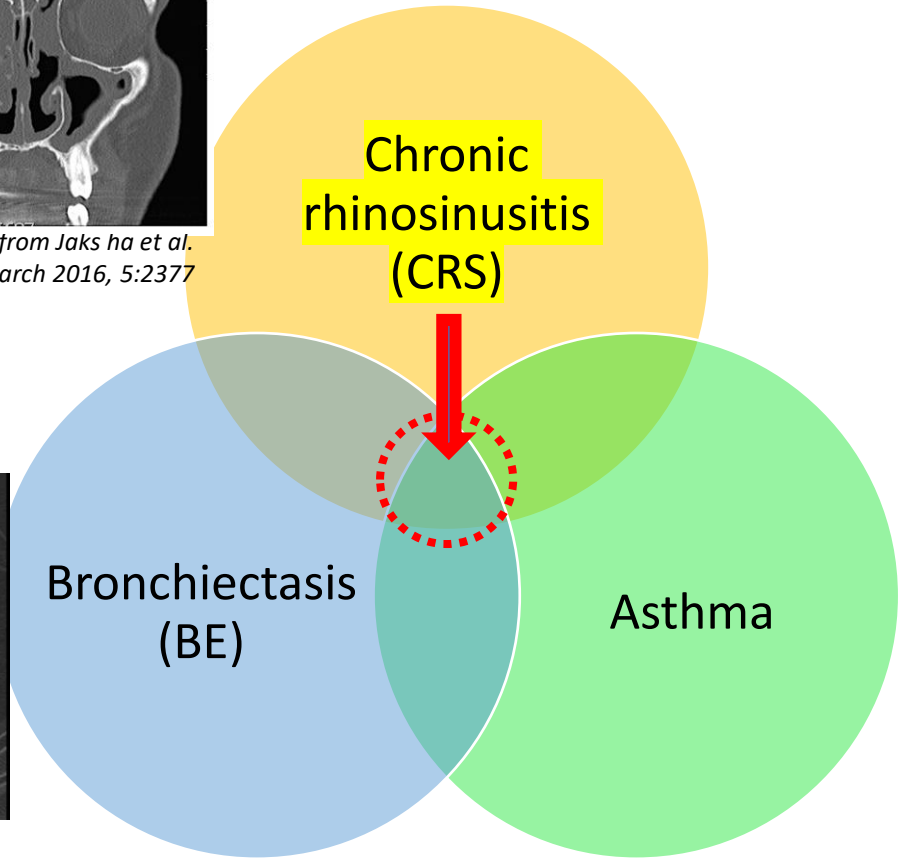

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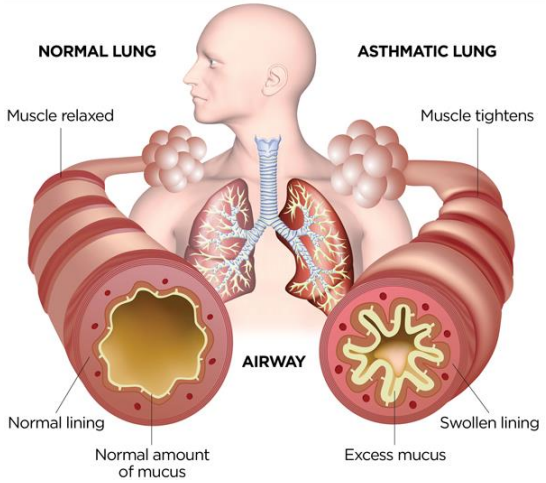


Normal vs asthma lung. Image from AAFA.org Access Dec 12 2021

CRS in patients with asthma and BE

- Limited studies
- In a study with cohort 176 asthma-CRS patient, 40% had bronchiectasis on CT chest. Patient with bronchiectasis had more nasal polyp, higher LMK score, more frequent asthma exacerbation, lower FEV1, and higher peripheral eosinophil count. *(Sheng et al. BMJ Pulm Med 2021)*
- The impact of CRS in asthma and bronchiectasis patient has not been well characterized.

Summary of background

- Bronchiectasis is common in severe asthma and associated with poorer outcome
- CRS is common in bronchiectasis and asthma. The impact of CRS on bronchiectasis, and asthmatic with bronchiectasis is not well known.
- Bronchiectasis is characterized by neutrophilic inflammation, but a subset can be eosinophilic. This may be associated with more severe disease. The endotype of bronchiectasis with comorbid CRS or asthma is not well characterized.

Research Questions

1. What is the relationship of CRS in patient with asthma and bronchiectasis? Is there an increase healthcare utilization in patients with asthma and bronchiectasis (+) vs (-) CRS?
   - Retrospective study, EDW

2. Is there a difference in quality of life (QoL) in patient with asthma and bronchiectasis (+) CRS vs (-) CRS
   - Prospective study, Questionnaires

3. Is there a difference in the type of inflammation of nasal lavage and sputum in pt with asthma and bronchiectasis (+) CRS vs (-) CRS
   - Prospective study, nasal lavage and sputum

Study Design 1 : BE confirmed by CT chest

All Electronic Data Warehouse (EDW) between 1988-2021

Dx of asthma without bronchiectasis by ICD 9/10 AND at least one CT chest
All EDW n = 6628

Exclusion:

- Cystic fibrosis,
- Primary ciliary dyskinesia,
- EGPA,
- COPD at the time of asthma dx

Baseline Characteristics (1/3): Higher prevalence of bronchiectasis, female sex, white race in patient with CRS

Table 1. Baseline characteristics of all patients with asthma and CT chest at least 6 months from asthma diagnosis (n=5038)			
Characteristics*	Without CRS n= 3059	With CRS n= 1979	P-value**
Bronchiectasis	471 (15.4)	496 (25.1)	<0.0001
Mean age (SD)	60.7 (16.6)	60.2 (14.3)	0.2985
Female	2120 (69.3)	1425 (72.0)	0.0402
Race			
White	1730 (66.2)	1079 (71.7)	0.0001
Black	580 (23.0)	257 (18.0)	
Others	(10.8)	(10.2)	
Mean BMI (SD)	31.2 (8.6)	30.5 (8.0)	0.0023
Smoking			
Current smoker	326 (11.4)	141 (7.3)	0.0001
Former smoker	770 (27.0)	485 (25.1)	
Never smoker	1759 (61.6)	1309 (67.7)	

Abbreviation: ….
* N() or otherwise indicated.
**P-values for the comparison between groups with and without CRS based on $\chi 2$ or T-test

Baseline Characteristics (2/3) Cont'd : Increased comorbidities are associated with presence of CRS

Table 1. Baseline characteristics by CRS status: All patients with asthma and CT chest at least 6 months from asthma diagnosis (n=5038)			
Characteristics*	Without CRS n= 3059	With CRS n= 1979	P-value**
Bronchiectasis	471 (15.4)	496 (25.1)	<0.0001
Comorbidities			
Allergic rhinitis	1358 (44.4)	1499 (75.7)	0.0001
ASA allergy	238 (7.8)	214 (10.8)	0.0002
Humoral def (IgA def, Ab def, CVID)	151 (4.9)	228 (11.5)	0.0001
Sleep Apnea	920 (30.1)	704 (35.6)	0.0001
GERD	1775 (58.0)	1454 (73.5)	0.0001
ABPA	21 (0.68)	30 (1.5)	0.0041
Autoimmune diseases (RA, Sjogrens, Lupus, Sclerosis)	337 (11.0)	277 (14.0)	0.0016
Sarcoidosis	74 (2.4)	43 (2.2)	0.5708

Abbreviation: ….
* N() or otherwise indicated.
**P-values for the comparison between groups with and without CRS based on $\chi 2$ or T-test

Baseline Characteristics (3/3) Cont'd: Increased use of medication, OCS, antibiotics, and ED/hospitalization seen in patients with CRS

Table 1. Baseline characteristics by CRS status: All patients with asthma and CT chest at least 6 months from asthma diagnosis (n=5038)			
Characteristics*	Without CRS n= 3059	With CRS n= 1979	P-value**
Bronchiectasis	471 (15.4)	496 (25.1)	<0.0001
Medication use associated with respiratory disease			
SABA use	2306 (75.4)	1565 (79.1)	0.0024
LAMA use	262 (8.6)	224 (11.3)	0.0012
ICS/LABA use	1034 (33.8)	892 (45.1)	0.0001
ICS use	1894 (61.9)	1443 (72.9)	0.0001
OCS use	1116 (36.5)	1043 (52.7)	0.0001
OCS use >= 2	653 (21.3)	696 (35.2)	0.0001
OCS use >=5	177 (5.8)	290 (14.6)	0.0001
Antibiotic use	1009 (33.0)	1102 (55.7)	0.0001
Antibiotic use >=2	426 (13.9)	735 (37.1)	0.0001
Antibiotic use >=5	56 (1.8)	234 (11.8)	0.0001
ED/Hospitalization	1574 (51.5)	1135 (57.4)	0.0001
ED/Hospitalization >=2	1005 (32.8)	747 (37.5)	0.0007
ED/Hospitalization >=5	345 (11.3)	303 (15.3)	0.0001

Abbreviation: ….

* N() or otherwise indicated.

**P-values for the comparison between groups with and without CRS based on $\chi 2$ or T-test

Result (1/4): Increased OCS use seen in patients with CRS and Asthma+BE

Percentage (%) of 5 year oral corticosteroid (OCS) use associated with respiratory exacerbation

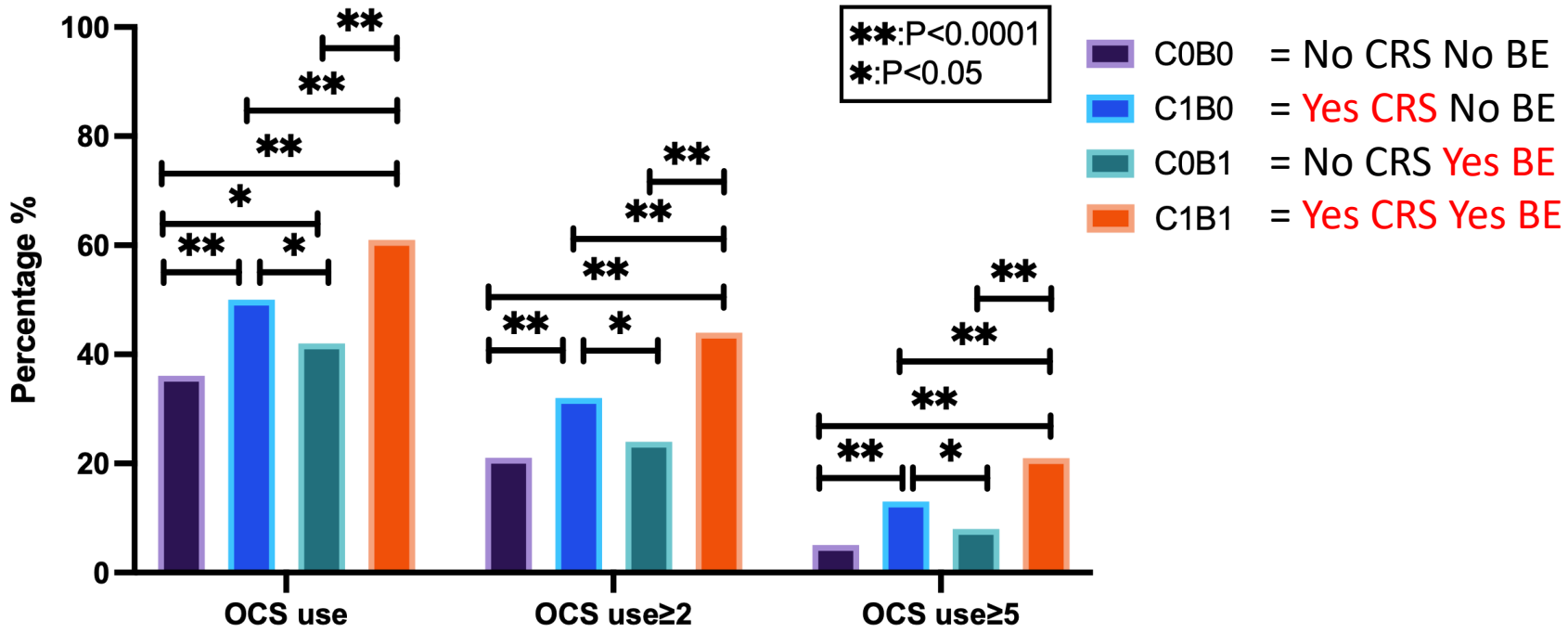


Table. 5 year OCS use by CRS and BE					
	C0B0	C1B0	C0B1	C1B1	P value
n	2588	1483	471	496	
OCS use	920 (35.6)	738 (49.8)	196 (41.6)	305 (61.5)	<0.0001
OCS use >= 2	540 (20.9)	476 (32.1)	113 (24.0)	220 (44.3)	<0.0001
OCS use >=5	139 (5.4)	187 (12.6)	38 (8.07)	103 (20.8)	<0.0001

Result (2/4): Increased Abx use was seen in patients with CRS and Asthma+BE

Percentage (%) of 5 year antibiotic use associated with respiratory exacerbation

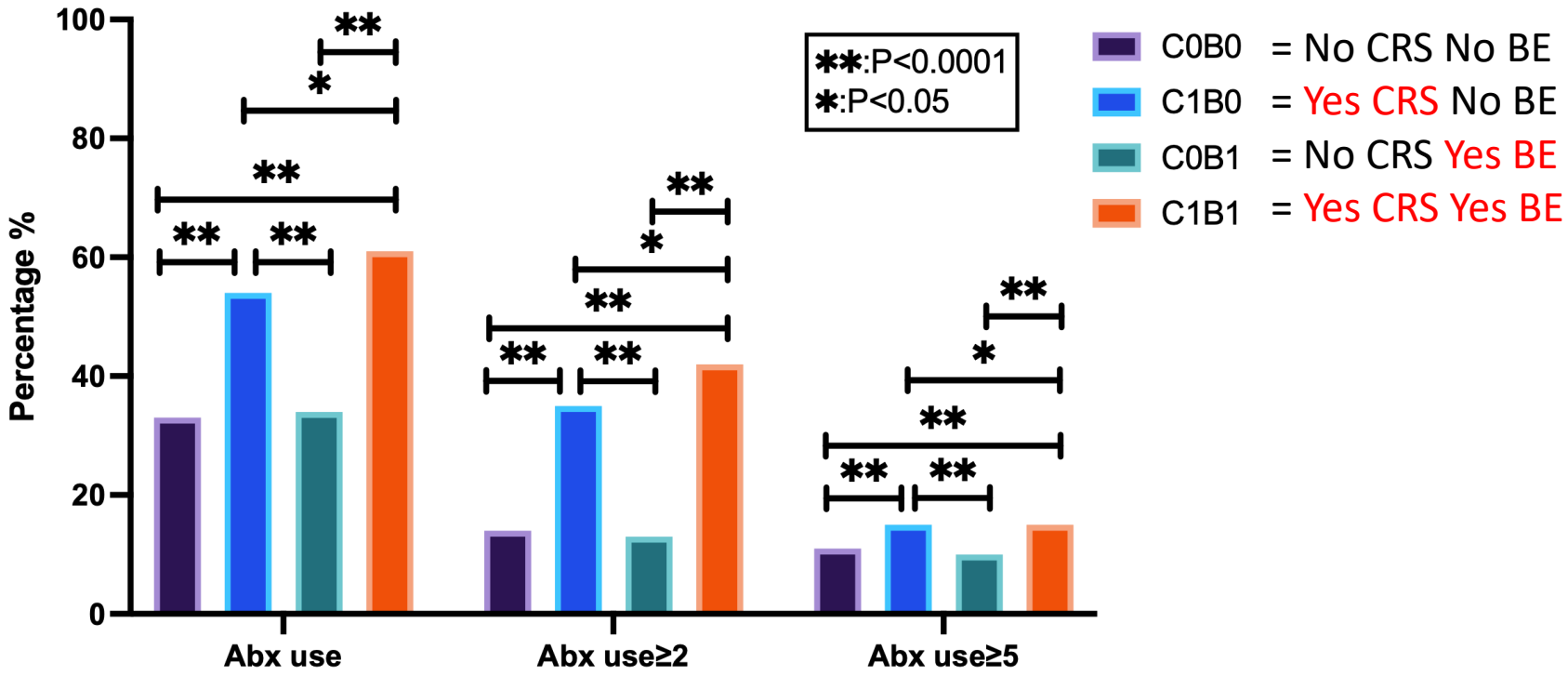


Table. 5 Year Antibiotic use by CRS and BE					
	C0B0	C1B0	C0B1	C1B1	P value
n	2588	1483	471	496	
Antibiotic use	848 (32.8)	797 (53.7)	161 (34.2)	305 (61.5)	<0.0001
Antibiotic use >=2	363 (14.0)	525 (35.4)	63 (13.4)	210 (42.3)	<0.0001
Antibiotic use >=5	45 (1.7)	161 (10.9)	11 (2.3)	73 (14.7)	<0.0001

Result (3/4): Increased ED/Hospitalization was seen in pt with CRS and asthma+BE

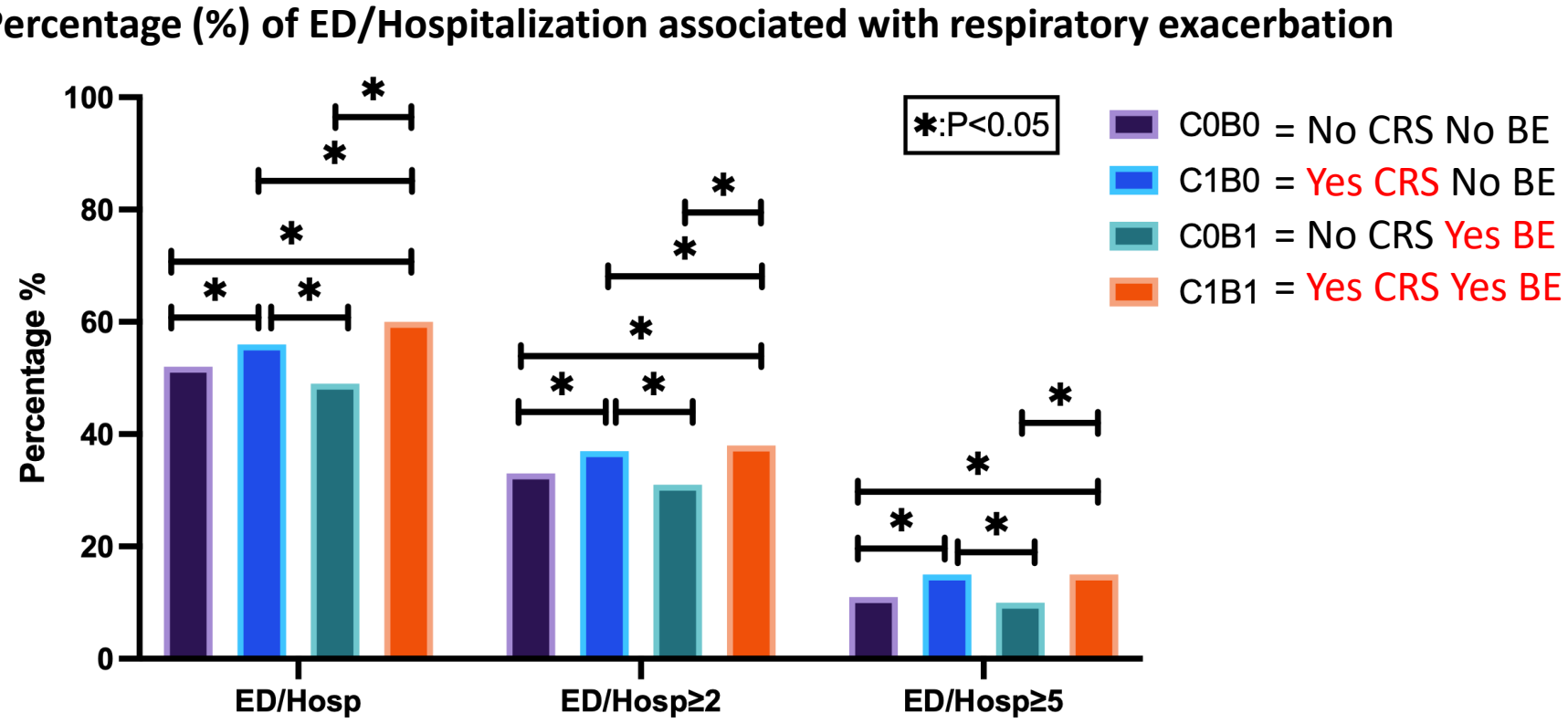


Table. 5 Year ED/Hospitalization by CRS and BE

	C0B0	C1B0	C0B1	C1B1	P value
n	2588	1483	471	496	
ED/Hospitalization	1341 (51.8)	837 (56.5)	233 (49.5)	298 (60.1)	0.0002
ED/Hospitalization >=2	860 (33.2)	552 (37.2)	145 (30.8)	190 (38.3)	0.0054
ED/Hospitalization >=5	296 (11.4)	227 (15.3)	49 (10.4)	76 (15.3)	0.0005

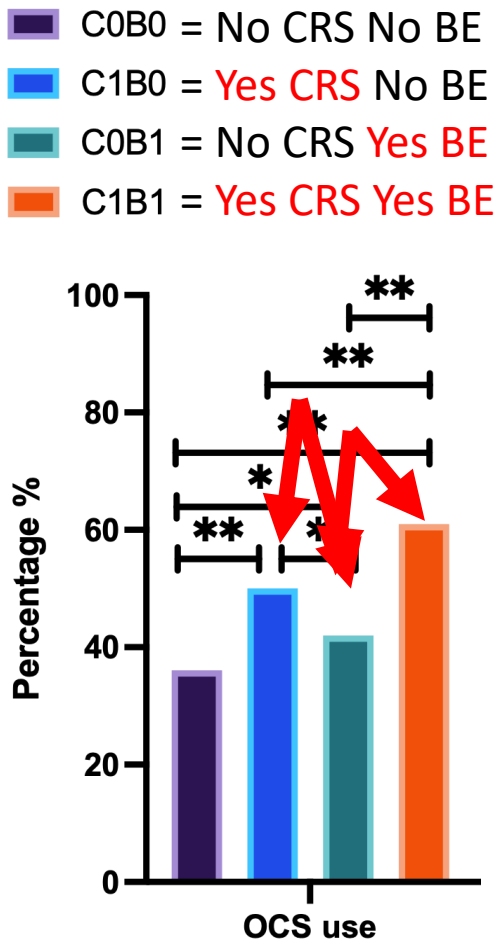
Result (4/4): Multivariate analysis controlling for age, sex, and race

Asthma+BE WITH CRS **(C1B1)** compared to Asthma+BE WITHOUT CRS **(C0B1)**, had an increased **Odds Ratio** of

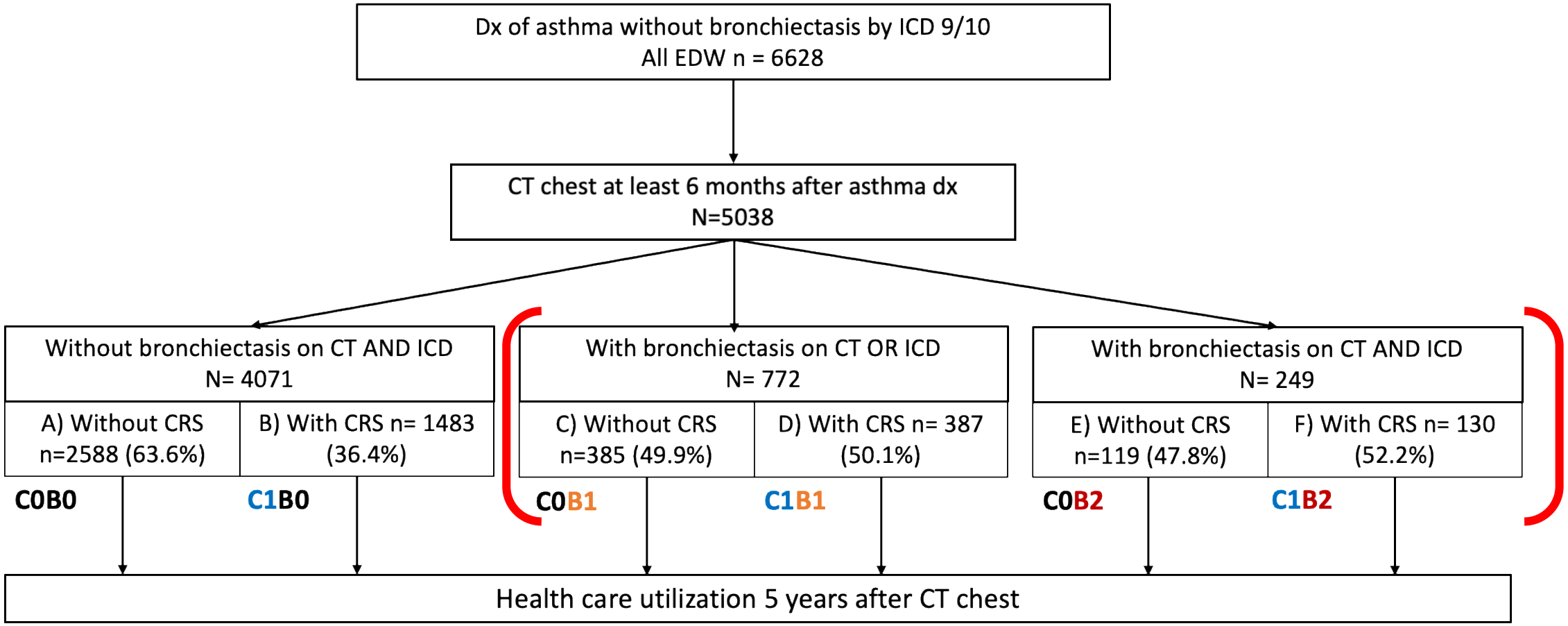
- OCS use of **2.3** (95% CI, 1.7-2.9; p<0.0001)
- Antibiotics use of **3.0** (95% CI, 2.3-3.9; p<0.0001)
- ED visit or hospitalizations of **1.6** (95% CI, 1.2-2.1; p=0.0004)

Asthma-BE with CRS **(C1B0)** compared to Asthma+BE without CRS **(C0B1),** had an increased **Odds Ratio** of

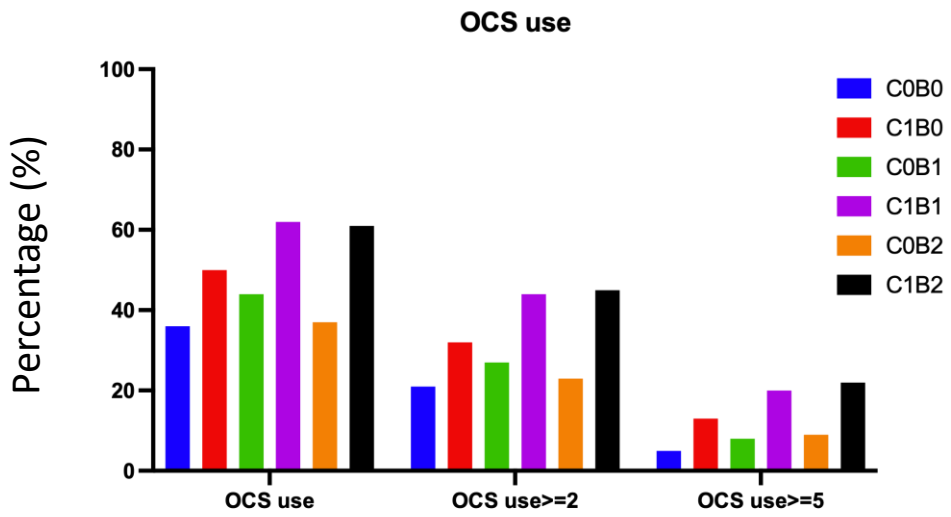
- OCS use of **1.4** (95% CI, 1.1-1.7; p=0.0028)
- antibiotics use of **2.1** (95% CI, 1.7-2.6; p<0.0001)
- ED visit or hospitalizations of **1.4** (95% CI, 1.2-1.7; p=0.003)

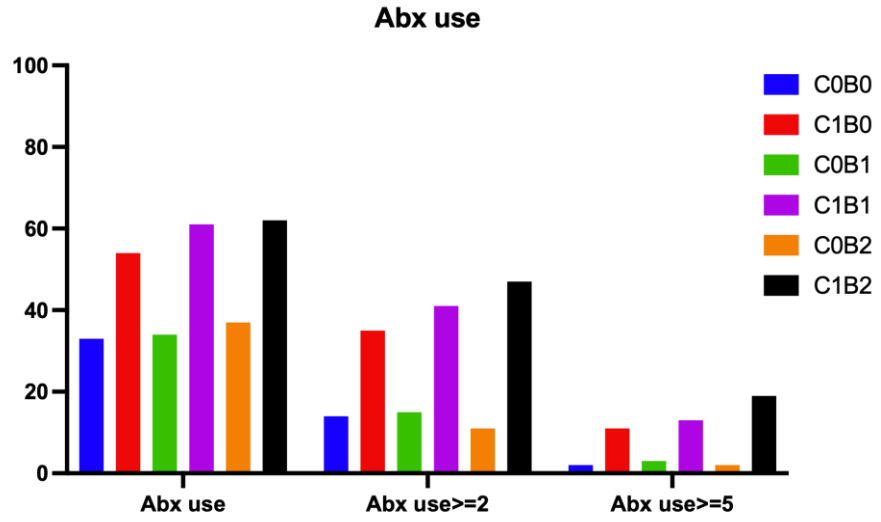


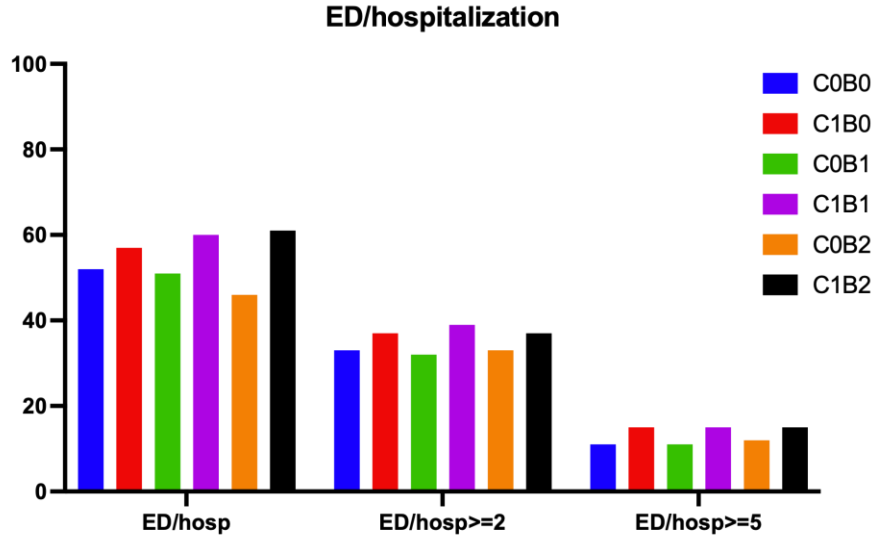
Study design 2: BE defined by having BOTH ICD and CT chest read.



Result: Similar outcome in patient with BE from both ICD and CT diagnosis.







In Summary…

- CRS is common in patient with asthma and BE, about 50% in our cohort.
- There is an increased 5 year OCS use, Abx use, and ED/hospitalization associated with presence of CRS in patients with asthma and BE.
- The presence of CRS in patient with asthma and BE identifies a subset of patients with high healthcare utilization
- CRS is an important comorbidities to screen in patient with asthma and BE

Limitation/In Progress

- Retrospective chart review
- CRS and asthma diagnosis based on ICD and CPT code
- Nasal polyp?
- Eosinophilic phenotype – peripheral eosinophil, total IgE, skin test, FENO?

Future Studies

1. Does the presence of CRS in asthmatic increases risk of development of bronchiectasis? Is there an increase healthcare utilization patients with asthma and bronchiectasis (+) vs (-) CRS?
   - Retrospective study, EDW

2. Is there a difference in quality of life (QoL) in patient with asthma and bronchiectasis (+) CRS vs (-) CRS
   - Prospective study, Questionnaires

3. Is there a difference in the type of inflammation of nasal lavage and sputum in pt with asthma and bronchiectasis (+) CRS vs (-) CRS
   - Prospective study, nasal lavage and sputum

Questions?

Thank you for your attention

Acknowledgement

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- Northwestern Feinberg School of Medicine, Division of Allergy and Immunology

- Which of the following statement is incorrect?
  A. Bronchiectasis is common in severe asthma and is associated with worse outcome
  B. Bronchiectasis is characterized predominantly by type 2 inflammation
  C. Non-cystic bronchiectasis is a heterogeneous disease from variety of etiologies
  D. Bronchiectasis is characterized by fixed irreversible dilation of the airway

- Which of the following statement is incorrect?
  A. Chronic rhinosinusitis is predominantly characterized by type 2 inflammation in western countries
  B. Bronchiectasis is prevalent in patients with chronic rhinosinusitis
  C. United airway disease hypothesize that upper airway disease and lower airway disease are connected by similar inflammatory process
  D. Bronchiectasis is more common in CRSsNP than CRSwNP.