Clinical significance of acute infectious exacerbations in COPD

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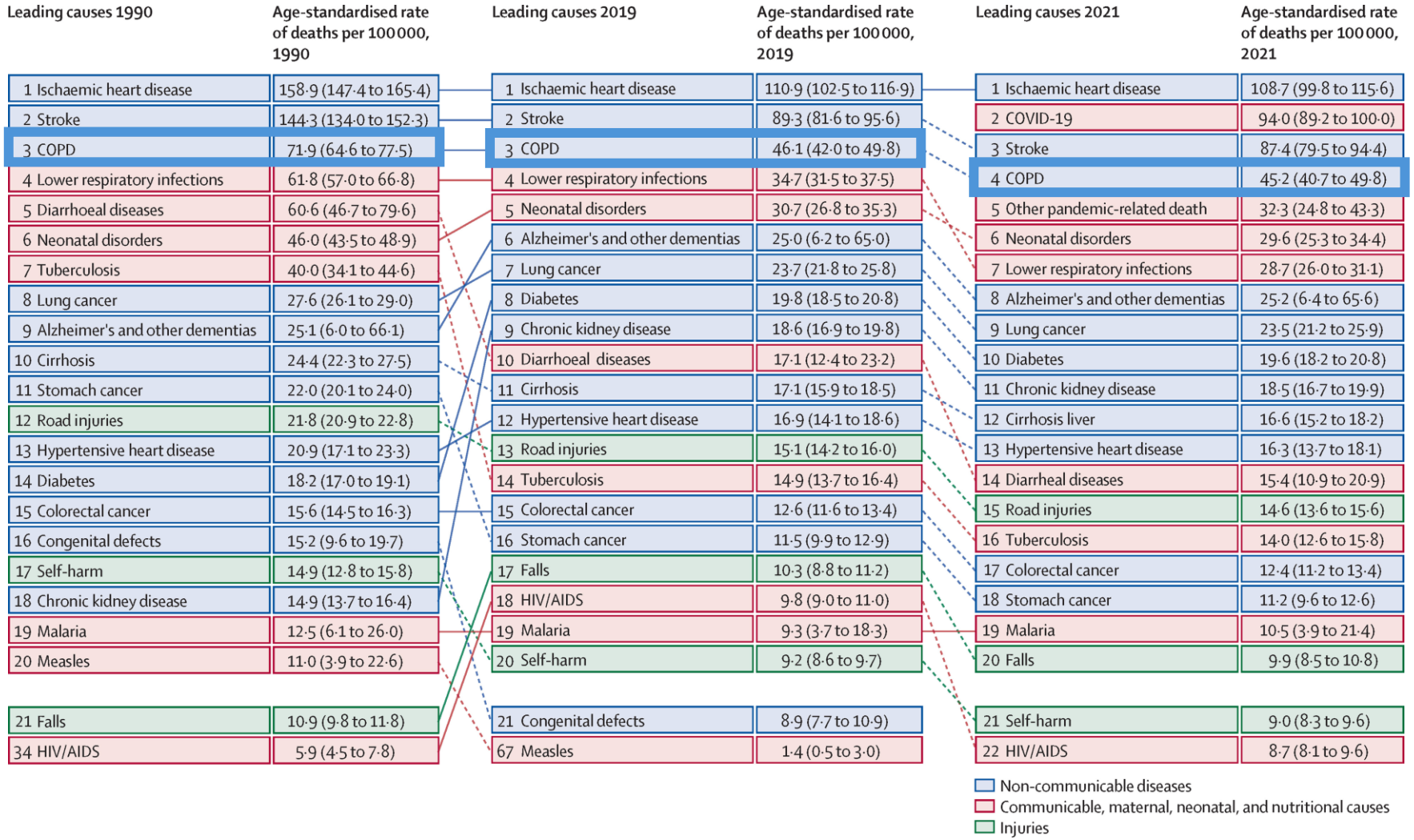
백문성

Leading causes of global deaths

Global Burden of Disease Study 2019

- 212.3 million prevalent cases
- **3.3 million deaths**



The Lancet 2024 Vol. 403 Issue 10440 Pages 2100-2132

2023년 사망원인통계 결과

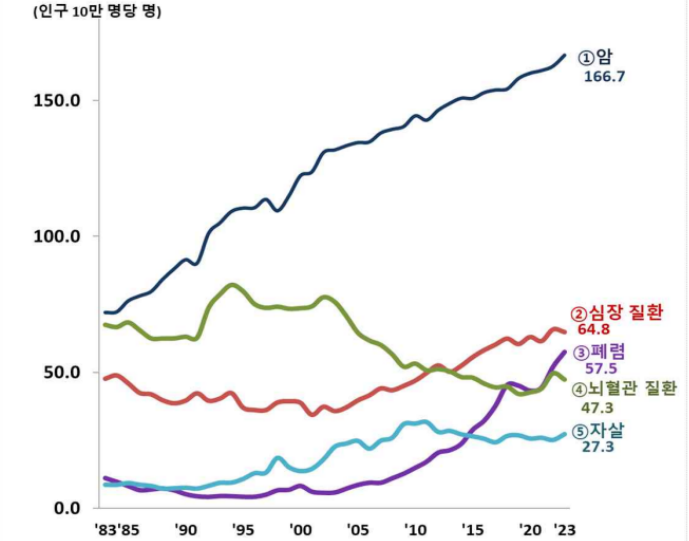
3대 사망원인은 암, 심장 질환, 폐렴 (전체 사망의 41.9%)

○ 10대 사망원인은 악성신생물(암), 심장 질환, 폐렴, 뇌혈관 질환, 고의적 자해(자살), 알츠하이머병, 당뇨병, 고혈압성 질환, 패혈증, 코로나19 순임.

(단위: 인구 10만 명당 명)

순위	사망원인	사망률	'22년 순위 대비
1	악성신생물(암)	166.7	-
2	심장 질환	64.8	-
3	폐렴	57.5	⬆(+1)
4	뇌혈관 질환	47.3	⬆(+1)
5	고의적 자해(자살)	27.3	⬆(+1)
6	알츠하이머병	21.7	⬆(+1)
7	당뇨병	21.6	⬆(+1)
8	고혈압성 질환	15.6	⬆(+1)
9	패혈증	15.3	⬆(+2)
10	코로나19	14.6	⬇(-7)

<사망원인 순위 추이>



COPD?

Definition of COPD exacerbations

COPD 진료지침 2024

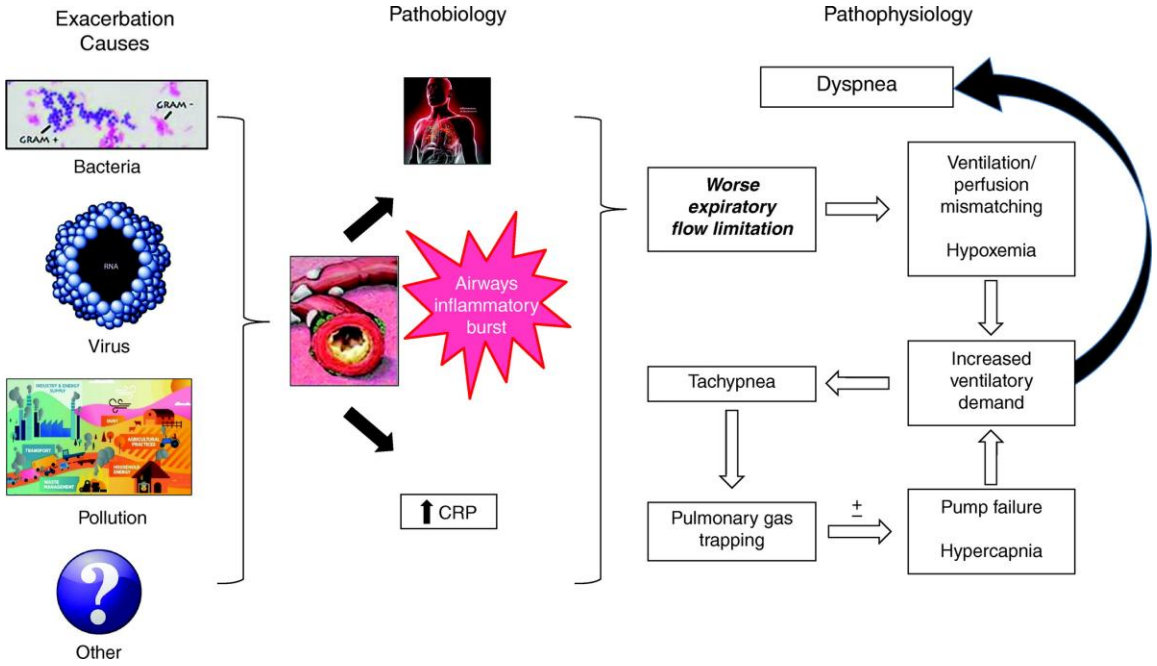
- COPD 환자의 기본적인 **호흡기증상이 매일-매일의 변동범위를 넘어서** 치료약제의 추가가 필요할 정도로 급격히 악화된 상태
- 분류
  - 경증 악화: **속효성** 기관지확장제 치료만 필요한 경우
  - 중등증 악화: 속효성 기관지확장제와 **항생제 또는 경구스테로이드** 치료가 필요한 경우
  - 중증 악화: **응급실 방문이나 입원이** 필요한 악화이며 급성 호흡부전을 동반할 수 있다.

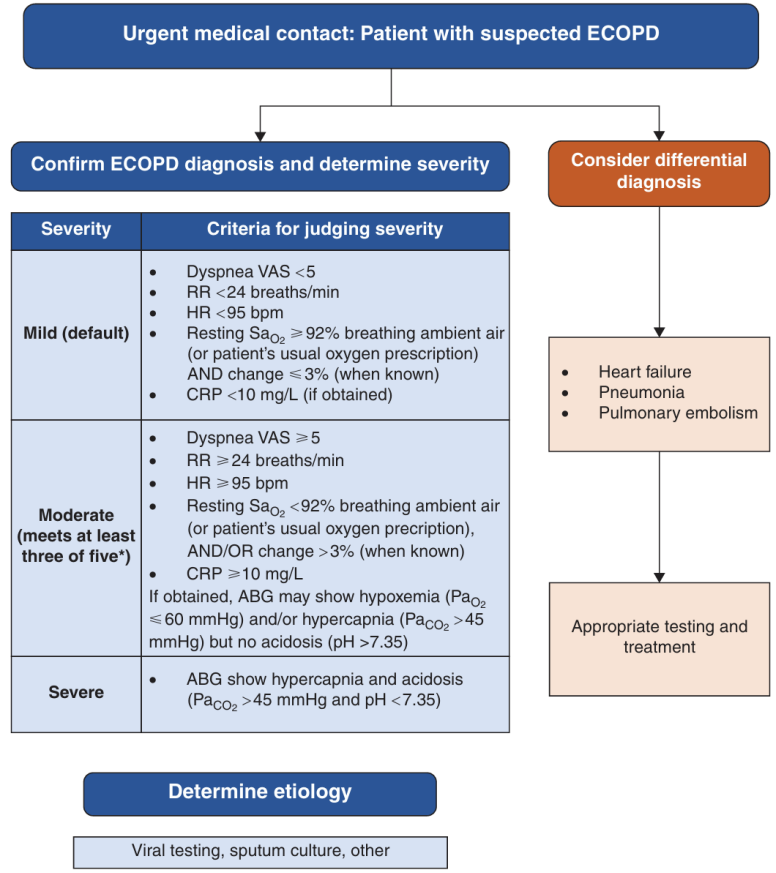
The Rome Proposal 2021

- In a patient with COPD, an exacerbation is an event characterized by **dyspnea and/or cough and sputum that worsen over ≤14 days**, which may be accompanied by **tachypnea and/or tachycardia** and is often associated with **increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways**

COPD 진료지침 2024
Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258.

Definition of COPD exacerbations





Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258.

Infectious causes of AECOPD

- Most exacerbations of COPD are caused by viral or bacterial infection.

Table 2 Microbial pathogens in exacerbations of COPD

Pathogen class	Proportion of exacerbations	Specific species	Proportion of class of pathogens
Bacteria	40%–50%	Nontypeable *Haemophilus influenzae*	30%–50%
		Streptococcus pneumoniae	15%–20%
		Moraxella catarrhalis	15%–20%
		Pseudomonas spp. and *Enterobacteriaceae*	Isolated in very severe COPD, concomitant bronchiectasis, recurrent exacerbations
		Haemophilus parainfluenzae	Isolated frequently, pathogenic significance undefined
		Haemophilus hemolyticus	Isolated frequently, pathogenic significance undefined
		Staphylococcus aureus	Isolated infrequently, pathogenic significance undefined
Viruses	30%–40%	*Rhinovirus*	40%–50%
		Parainfluenza	10%–20%
		Influenza	10%–20%
		RSV	10%–20%
		Coronavirus	10%–20%
		Adenovirus	5%–10%
Atypical bacteria	5%–10%	*Chlamydia pneumoniae*	90%–95%
		Mycoplasma pneumoniae	5%–10%

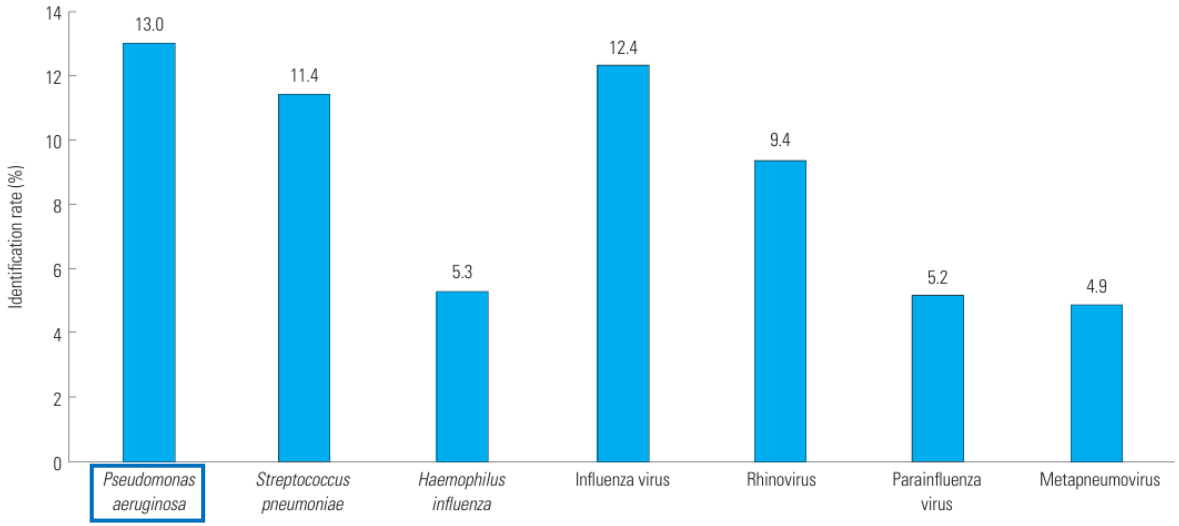


Fig. 1. Pathogen identification rate.

736 cases of **severe AECOPD** at the Korea University Guro Hospital (n=487)
2011 ~ 2017

Int J Chron Obstruct Pulmon Dis. 2008;3(1):31-44.
Yonsei Med J 2019 Feb;60(2):216-222

Bacteria as a cause of exacerbations

Table 1. Microbial Pathogens in COPD.*

Microbe	Role in Exacerbations	Role in Stable Disease
Bacteria		
Haemophilus influenzae	20–30% of exacerbations	Major role
Streptococcus pneumoniae	10–15% of exacerbations	Minor role
Moraxella catarrhalis	10–15% of exacerbations	Minor role
Pseudomonas aeruginosa	5–10% of exacerbations, prevalent in advanced disease	Probably important in advanced disease
Enterobacteriaceae	Isolated in advanced disease, pathogenic significance undefined	Undefined
H. haemolyticus	Isolated frequently, unlikely cause	Unlikely
H. parainfluenzae	Isolated frequently, unlikely cause	Unlikely
Staphylococcus aureus	Isolated infrequently, unlikely cause	Unlikely
Viruses		
Rhinovirus	20–25% of exacerbations	Unlikely
Parainfluenza virus	5–10% of exacerbations	Unlikely
Influenza virus	5–10% of exacerbations	Unlikely
Respiratory syncytial virus	5–10% of exacerbations	Controversial
Coronavirus	5–10% of exacerbations	Unlikely
Adenovirus	3–5% of exacerbations	Latent infection seen, pathogenic significance undefined
Human metapneumovirus	3–5% of exacerbations	Unlikely
Atypical bacteria		
Chlamydophila pneumoniae	3–5% of exacerbations	Commonly detected, pathogenic significance undefined
Mycoplasma pneumoniae	1–2% of exacerbations	Unlikely
Fungi		
Pneumocystis jiroveci	Undefined	Commonly detected, pathogenic significance undefined

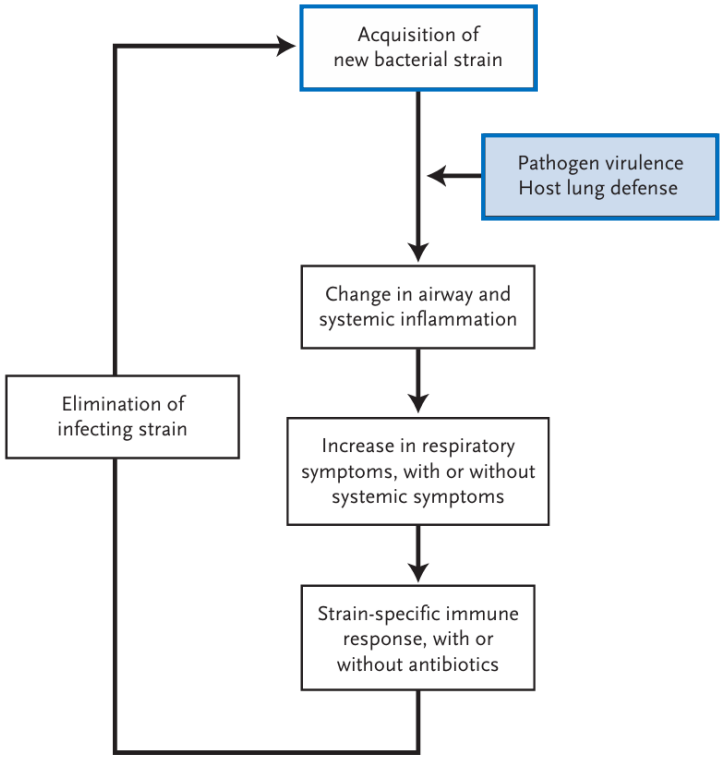


Figure 1. Proposed Model of the Pathogenesis of Bacterial Exacerbations in COPD.

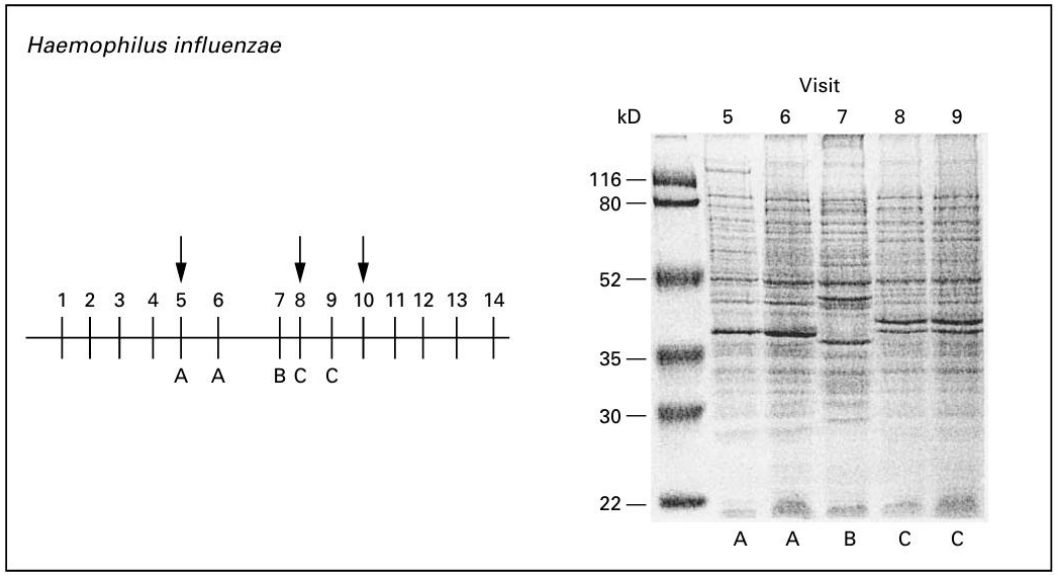
N Engl J Med. 2008 Nov 27;359(22):2355-65.

Acquisition of new strains of bacteria

- COPD (n=81), 1975 OPD visits, 374 exacerbations (56 months~)
- Molecular typing of sputum isolates: *H. influenzae, M. catarrhalis, S. pneumoniae, P. aeruginosa*

TABLE 2. CHARACTERISTICS OF 1975 COMPLETED CLINIC VISITS.

VARIABLE	VALUE
No. of visits during stable disease (%)	1601 (81.1)
No. of visits during exacerbations (%)	374 (18.9)
Total no. of visits/patient	
Mean	24.4
Range	2–65
No. of visits during exacerbations/patient	
Mean	4.6
Range	0–22
Mean no. of visits during exacerbations/patient/yr	2.1
Mean no. of days between visits	33.6



Timelines and molecular typing

Number: clinic visit
Arrow: exacerbation

N Engl J Med 2002;347:465-71.

Acquisition of new strains of bacteria

- Pathogenic bacteria: 601 of the 1827 visits (32.9%)
  - RR of AECOPD with pathogens: 1.44

TABLE 3. RELATIVE RISK OF AN EXACERBATION ACCORDING TO WHETHER A BACTERIAL PATHOGEN WAS ISOLATED.

PATHOGEN	FREQUENCY OF EXACERBATION		P VALUE	RELATIVE RISK (95% CI)*
	PATHOGEN	NO PATHOGEN		
	no. of exacerbations/ total no. of visits (%)			
Any pathogen	142/601 (23.6)	221/1226 (18.0)	<0.001	1.44 (1.24–1.68)
Haemophilus influenzae	77/375 (20.5)	286/1452 (19.7)	0.18	1.14 (0.94–1.38)
Moraxella catarrhalis	46/133 (34.6)	317/1694 (18.7)	<0.001	1.99 (1.52–2.62)
Streptococcus pneumoniae	13/52 (25.0)	350/1775 (19.7)	0.02	1.40 (1.05–1.87)
Pseudomonas aeruginosa	14/65 (21.5)	349/1762 (19.8)	0.66	1.09 (0.74–1.60)
Staphylococcus aureus	0/19 (0)	363/1808 (20.1)	0.007	0.15 (0.04–0.60)
Other gram-negative rods	6/56 (10.7)	357/1771 (20.2)	0.20	0.76 (0.49–1.16)

- New strains: 81 of 270 visits (33.0 %)
  - RR of AECOPD with new bacterial strain: 2.15

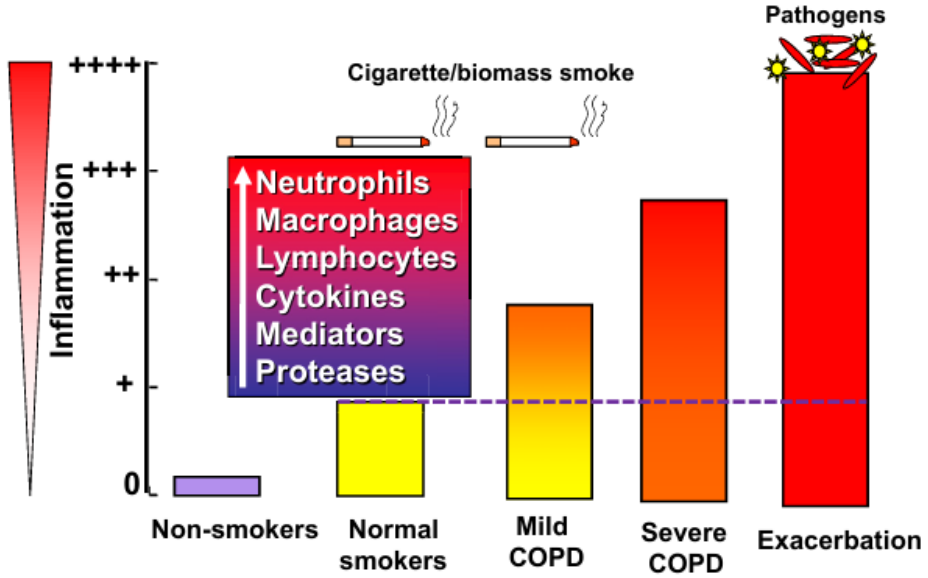
TABLE 4. RELATIVE RISK OF AN EXACERBATION ACCORDING TO WHETHER A NEW STRAIN OF BACTERIAL PATHOGEN WAS ISOLATED.

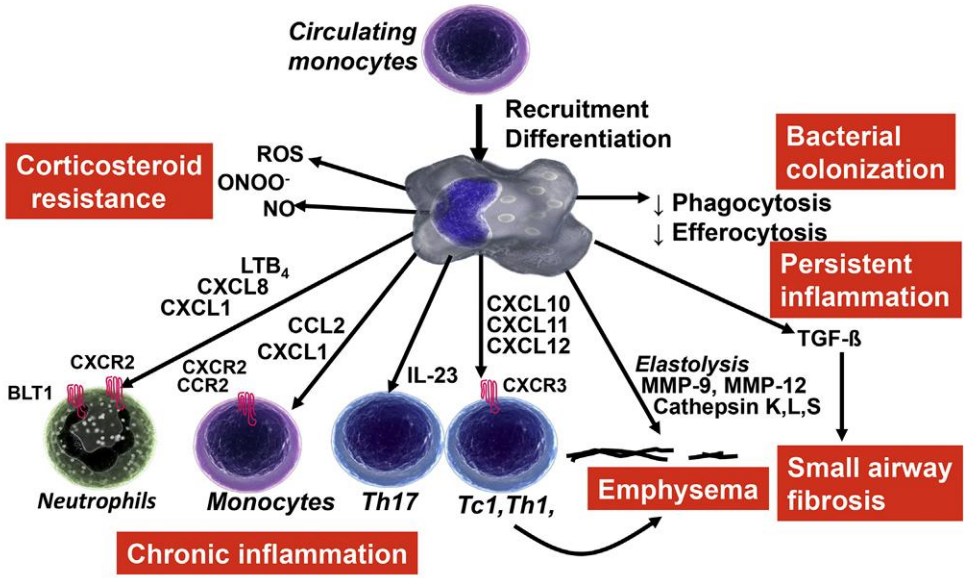
NEW STRAIN	FREQUENCY OF EXACERBATION		P VALUE	RELATIVE RISK (95% CI)*
	NEW STRAIN	NO NEW STRAIN		
	no. of exacerbations/ total no. of visits (%)			
Any strain	89/270 (33.0)	213/1385 (15.4)	<0.001	2.15 (1.83–2.53)
Haemophilus influenzae	38/145 (26.2)†	257/1503 (17.1)	<0.001	1.69 (1.37–2.09)
Moraxella catarrhalis	41/84 (48.8)	261/1571 (16.6)	<0.001	2.96 (2.39–3.67)
Streptococcus pneumoniae	8/25 (32.0)	294/1630 (18.0)	0.01	1.77 (1.14–2.75)
Pseudomonas aeruginosa	3/22 (13.6)‡	297/1631 (18.2)	0.38	0.61 (0.21–1.82)

- **Isolation of a new strain of a pathogen: significant increase in the frequency of exacerbation**

N Engl J Med 2002;347:465-71.

Inflammatory mechanisms in COPD





Central role of alveolar macrophages in patients with COPD

Inflammatory cells

- **Innate immunity:** neutrophils, macrophages, eosinophils, mast cells, natural killer cells, innate lymphoid cells, dendritic cells
- **Adaptive immunity:** T and B lymphocytes
- **Structural cells:** airway and alveolar epithelial cells, endothelial cells, fibroblasts

J Allergy Clin Immunol. 2016 Jul;138(1):16-27.

Host lung defense

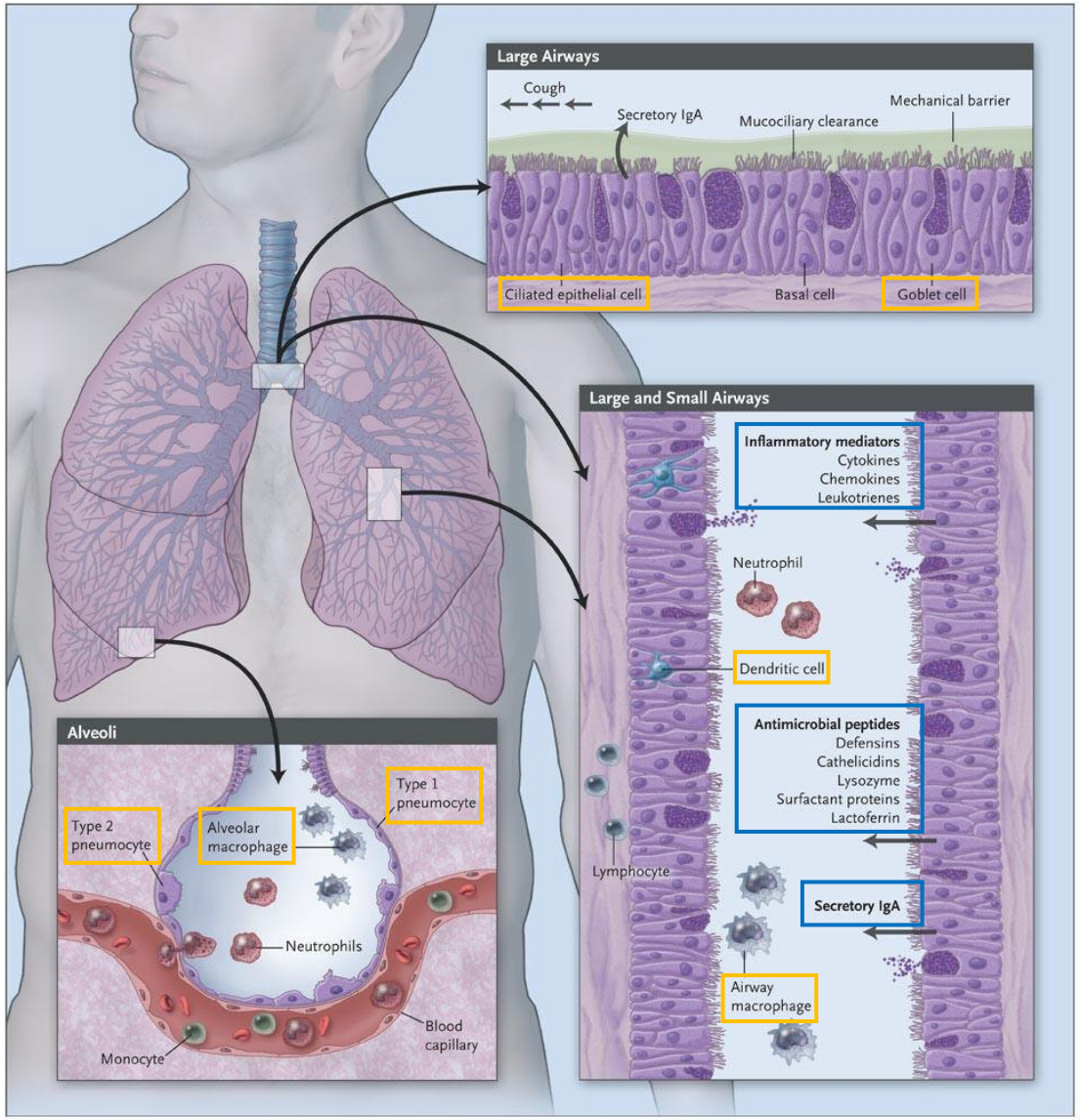


Table 2. Bacterial Ligands That Trigger Signal-Transduction Pathways in the Respiratory Tract through Pattern-Recognition Receptors.*

Pattern-Recognition Receptor	Bacterial Ligand	Bacterial Species
TLR1	—	*Streptococcus pneumoniae*
TLR2	P6, P2 porin, lipoproteins	*Haemophilus influenzae*
	Lipoteichoic acid, pneumolysin	*S. pneumoniae*
TLR4	Lipo-oligosaccharide	*H. influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa*
	Pneumolysin, lipoteichoic acid	*S. pneumoniae*
CD14	Lipo-oligosaccharide	*H. influenzae*
Lipopolysaccharide-binding protein	Lipo-oligosaccharide	*H. influenzae*
	Peptidoglycan	*S. pneumoniae*
TLR-5	Flagellin	*P. aeruginosa*
TLR-7	—	*H. influenzae*
TLR-9	CpG dinucleotides	*S. pneumoniae*
NOD 1, NOD 2	Ubiquitous surface protein A1	*M. catarrhalis*
	Peptidoglycan	*H. influenzae, S. pneumoniae*
Carcinoembryonic antigen-related cell-adhesion molecule 1	Ubiquitous surface protein A1	*M. catarrhalis*
Platelet-activating factor receptor	Pneumolysin, lipoteichoic acid	*S. pneumoniae*
	Ubiquitous surface protein A2	*M. catarrhalis*
C-reactive protein	Phosphorylcholine	*S. pneumoniae*

Innate immunity cells

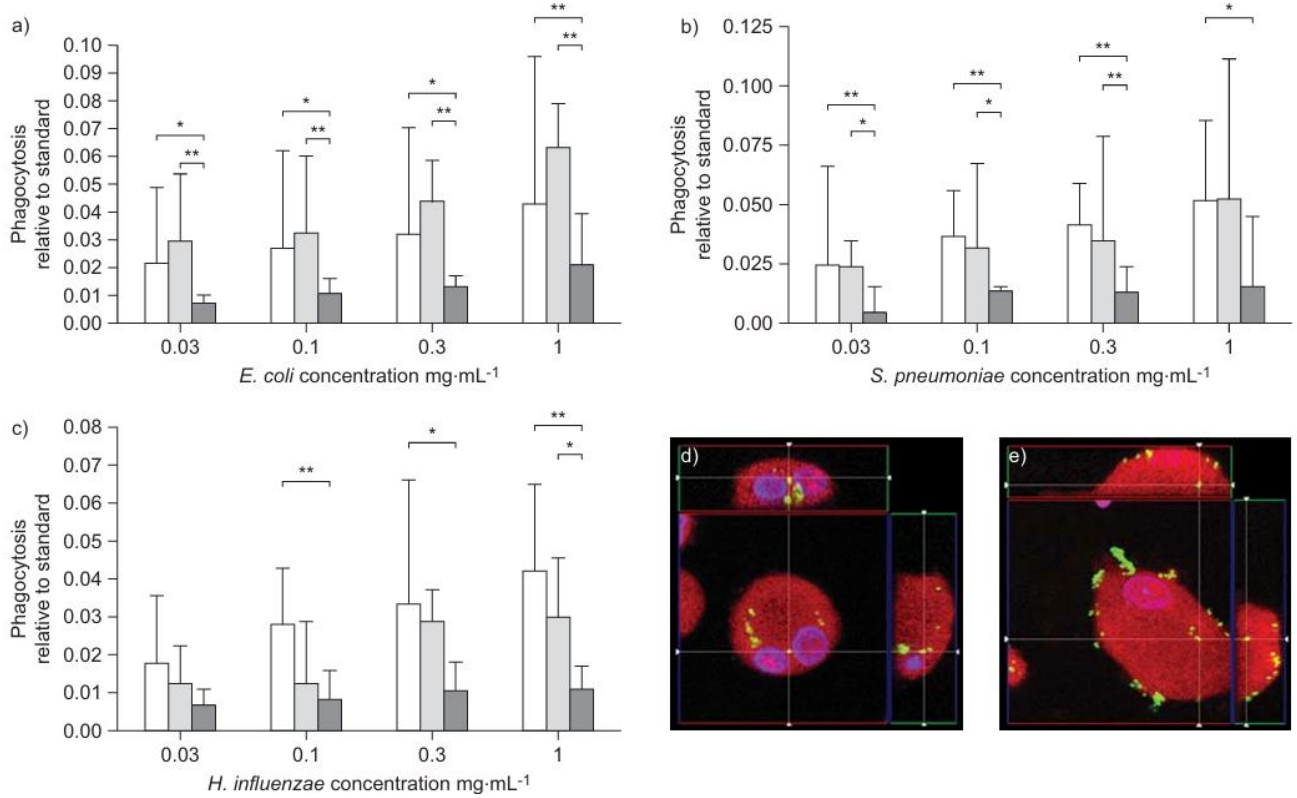
Secreted products

Defective macrophage phagocytosis of bacteria

- Alveolar macrophages: isolated from BALF
- Phagocytosis: assessed by fluorimetry and flow cytometry
- Receptor expression: measured by flow cytometry

TABLE 1 Study participant demographics

	Nonsmokers	Smokers	COPD
Subjects n	20	17	19
Age yrs	48±3	53±2	70±2¶,+
Sex M/F n	11/9	10/7	11/8
Smoking history pack-yrs#	0.0±0.0+	33.3±4.6	45.0±4.9¶
FEV1 L	3.3±0.15	2.9±0.3	1.2±0.1¶,+
FEV1 % pred	102.7±2.6	93.8±3.8	50.6±4.0¶,+
FVC L	4.2±0.2	3.8±0.3	2.4±0.3¶,+
FEV1/FVC	0.8±0.03	0.8±0.02	0.5±0.03¶,+



Monocyte-derived **macrophages from COPD patients showed reduced phagocytic responses** to S. pneumoniae and H. influenzae compared with nonsmokers and smokers.

- In **COPD**, **macrophage innate responses are suppressed**, potentially leading to bacterial colonisation and more frequent exacerbations.

Eur Respir J 2010; 35: 1039–1047

Impaired innate alveolar macrophage response

- Exacerbation-prone (n=29) vs non-exacerbation-prone (n=59)
- RML BAL to obtain alveolar macrophage (AM)
- AM: incubated with respiratory pathogens
- Elicited IL-8 and TNF-α: measured by microsphere flow cytometry

- Impaired innate responses of COPD AMs to respiratory pathogens

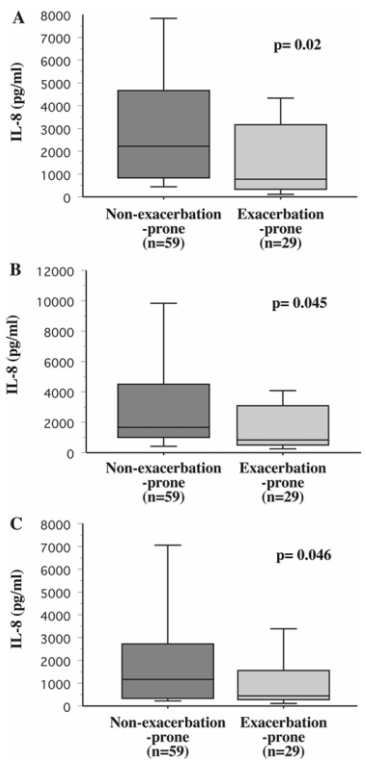
→ mediated by impaired TLR responses

→ exacerbations in COPD

H. influenzae

M. catarrhalis

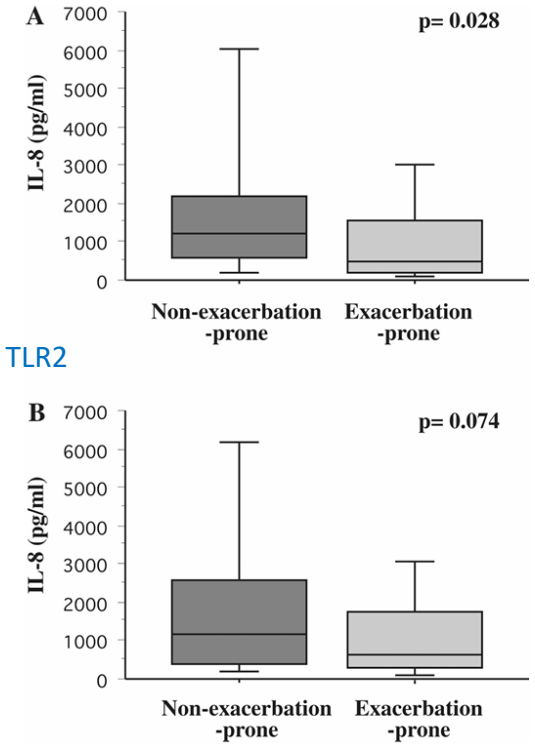
S. pneumoniae



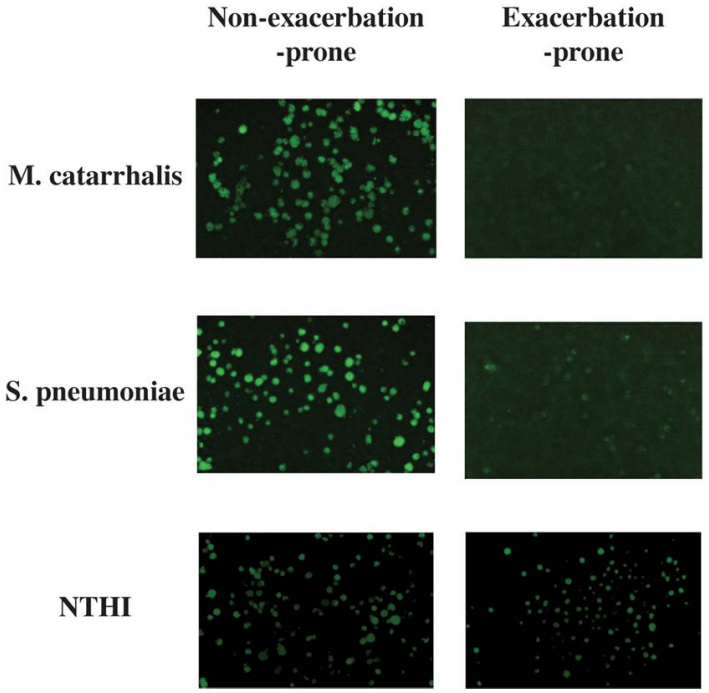
Bacterial induction of human alveolar macrophage IL-8 and COPD exacerbations

TLR4

TLR2



TLR2 and TLR4 ligand induction of human alveolar macrophage IL-8



Diminished TLR2 expression in exacerbation-prone donors

Thorax. 2014 Sep;69(9):811-8.

Vicious circle

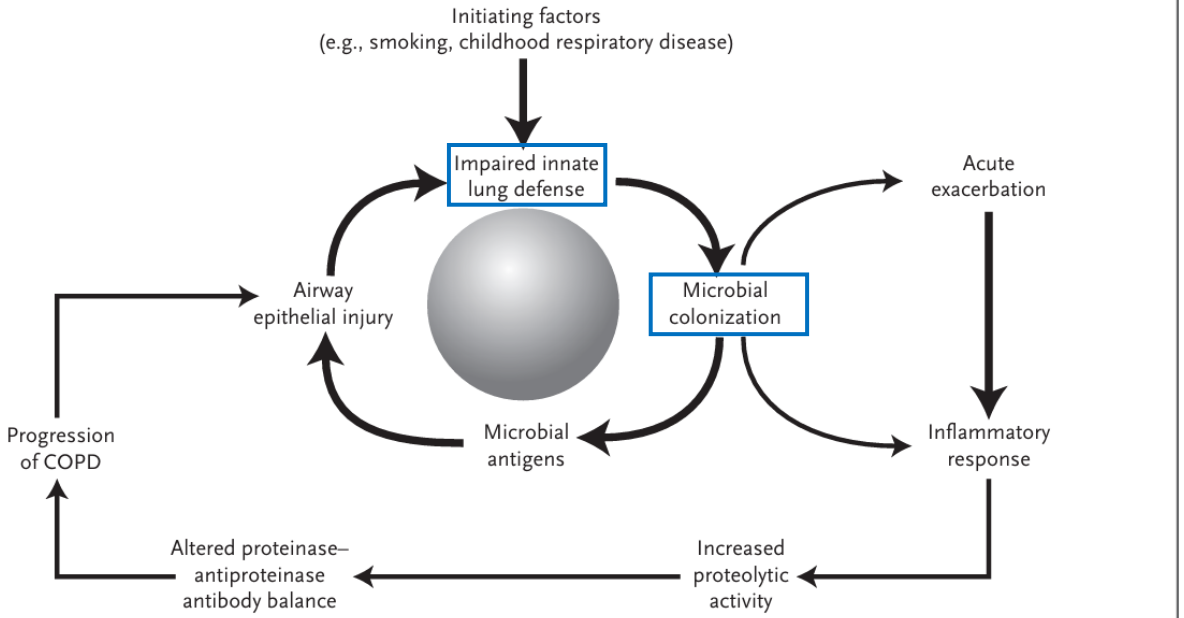


Figure 3. The Vicious-Circle Hypothesis of Infection and Inflammation in COPD.

After the initial insult impairs innate lung defense, microbial colonization perpetuates a cyclical sequence of events that contributes to the persistent inflammation and infection that are characteristic of COPD.

- Bacterial colonization

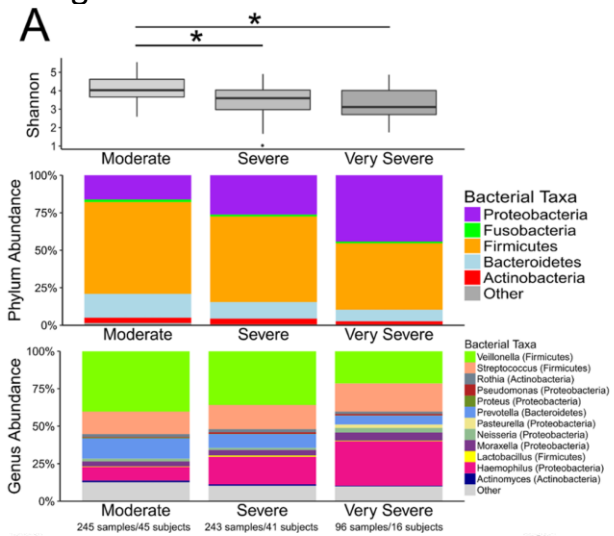
→ increased bacterial load (chronically colonized) in stable COPD

→ greater airway inflammation and increased risk of exacerbation

N Engl J Med 2002;347:465-71.

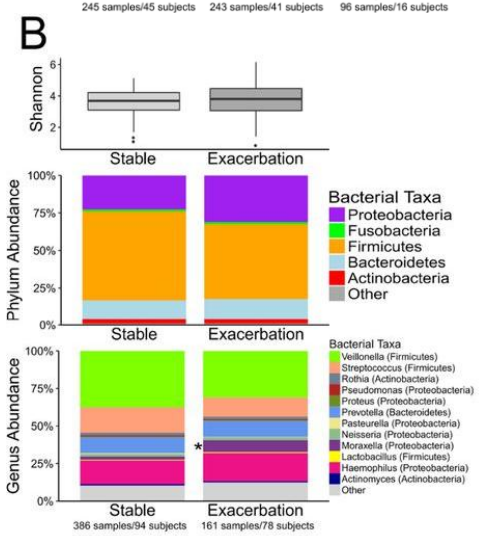
Microbiome changes during AECOPD

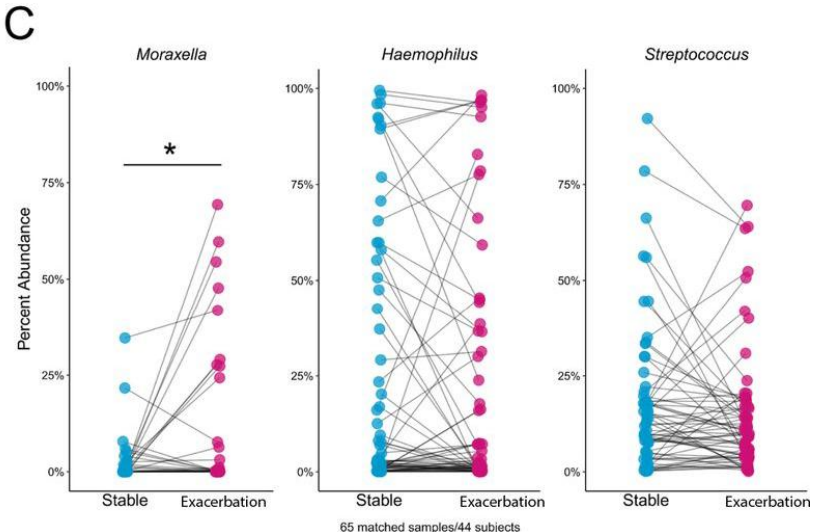
- **AERIS** study: 101 patients with COPD, 584 sputum samples, over 1 year
- lung microbiome at both stable and exacerbation time points



	Severe vs Moderate	Very Severe vs Moderate	Very Severe vs Severe
% Proteobacteria		↑*	↑*
% Bacteroidetes	↓*	↓*	
% Firmicutes			
% *Haemophilus*		↑*	
% *Prevotella*	↓*	↓*	
% *Veillonella*		↓*	↓*
% *Streptococcus*			
% *Moraxella*			

* : P-value < 0.05





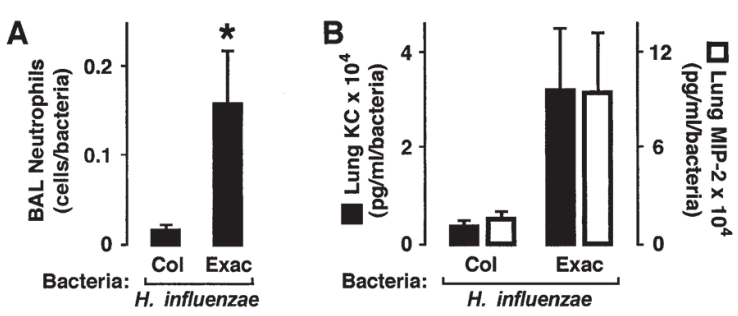
Disease severity↑
- Shannon diversity↓
- Haemophilus (Proteobacteria) ↑
- Prevotella (Bacteroidetes) and Veillonella (Firmicutes) ↓

At exacerbation
- Moraxella (Proteobacteria) ↑

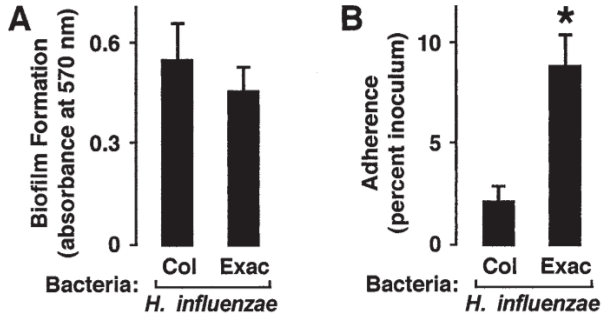
Thorax. 2018 May;73(5):422-430.

Host response to bacteria and susceptibility

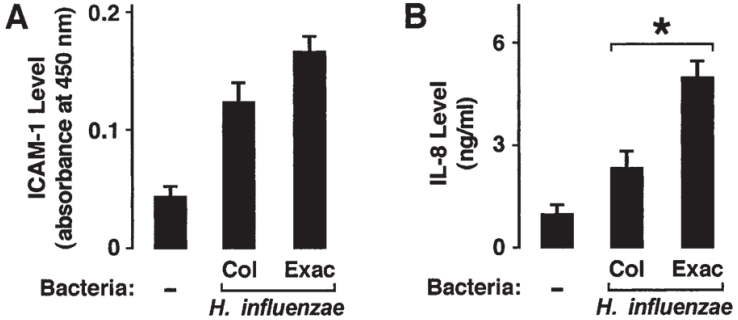
- Exacerbation strains vs. colonization strains of H. influenzae isolated from patients
- Bacterial strains were compared using an in vivo mouse model of airway infection



Increased induction of airway inflammation



Increased adherence to epithelial cells



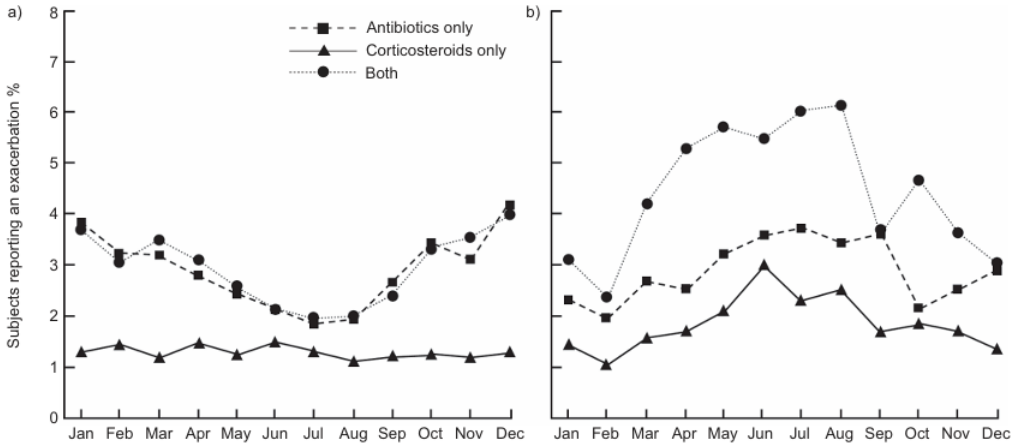
Increased induction of IL-8

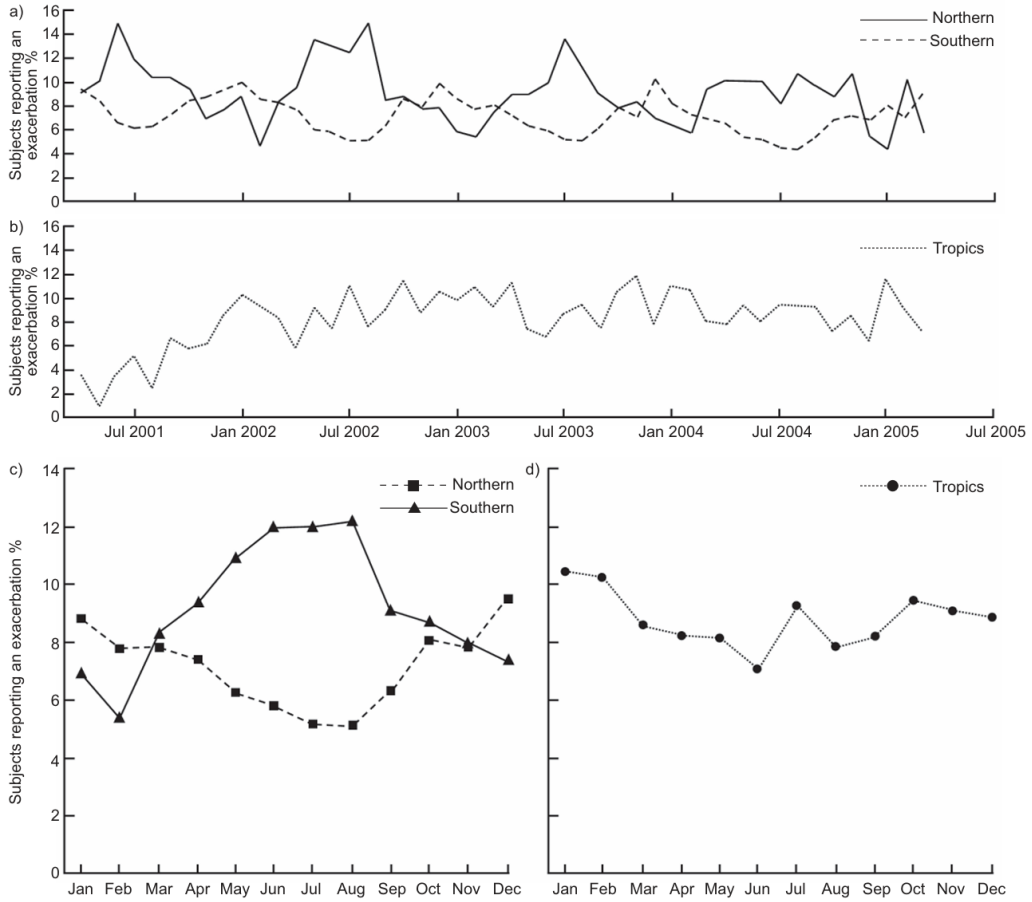
- In a mouse model, H influenzae strains associated with **AECOPD** induced **greater airway neutrophil recruitment** compared with **colonization** associated strains.

Am J Respir Crit Care Med. 2005 Jul 1;172(1):85-91.

Seasonality of AECOPD

- Data from the prospective, 3-yr TORCH study (n=6,112)
- Northern, southern regions and the tropics





- 2-fold increase of exacerbations in the winter months in the northern and southern regions
- No seasonal pattern in the tropics

Contributing factors
- **increased exposure to viral infections**
- increased host susceptibility
- greater time spent indoors
- reduced physical activity
- temperature-related reduction in lung function

Eur Respir J. 2012 Jan;39(1):38-45.

Common cold and AECOPD

- COPD (n=150), 1005 colds, 1493 exacerbations
- Diary cards: PEF, respiratory and coryzal symptoms, median 1,047 days
- **Cold, coryzal symptoms prior to the onset of exacerbation: 84% of cases**

TABLE 3 Relationships between colds and exacerbation frequency in chronic obstructive pulmonary disease[#]

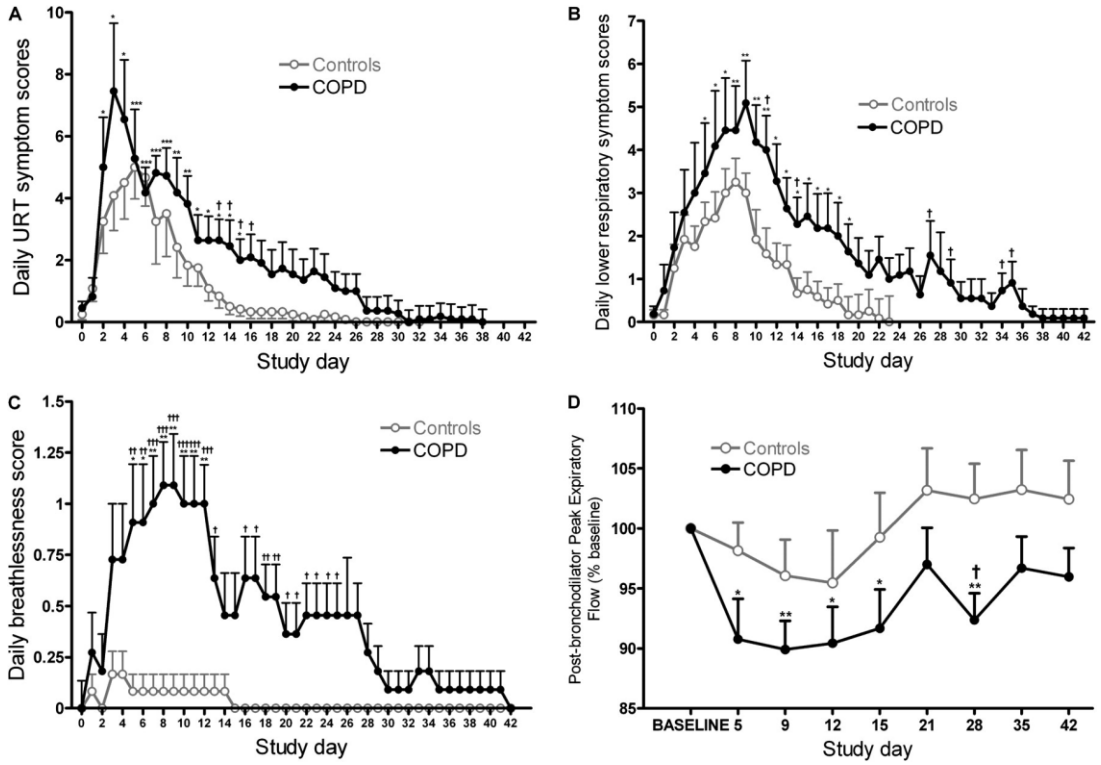
	Validated definition			Alternative definition		
	Infrequent exacerbators	Frequent exacerbators	p-value	Infrequent exacerbators	Frequent exacerbators	p-value
Exacerbation frequency ·yr^{-1}	1.55 (0.81–2.16)	3.83 (3.21–5.31)		1.31 (0.76–2.02)	3.45 (2.90–3.45)	
Total colds frequency ·yr^{-1}	0.94 (0.44–1.75)	1.73 (0.88–3.73)	0.003	0.95 (0.45–1.75)	1.73 (0.78–3.39)	0.016
Upper airway colds frequency ·yr^{-1}	0.44 (0.00–0.94)	0.74 (0.00–2.10)	0.131	0.63 (0.15–1.46)	0.92 (0.30–2.56)	0.172
Exacerbations associated with a cold ·yr^{-1}	0.45 (0.00–0.88)	0.95 (0.46–1.63)	<0.001	0.32 (0.00–0.54)	0.55 (0.00–1.08)	<0.001
Colds associated with exacerbation/ total colds ratio %	50 (11–80)	54 (33–80)	0.135	33 (3–50)	33 (17–60)	0.133

- Exacerbation frequency in COPD is associated with an increased frequency of acquiring the common cold

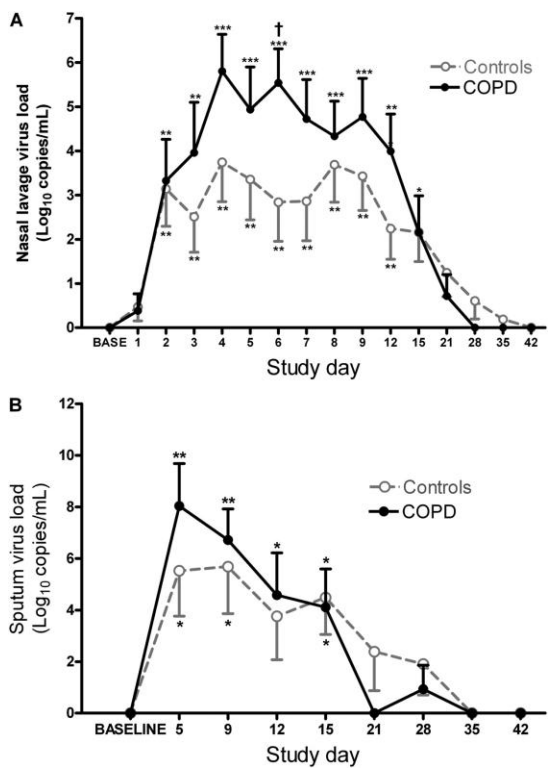
Eur Respir J 2005; 26: 846–852

Causal relationship between viral infection and AECOPD

- Experimental rhinovirus infection (n=13) vs. nonobstructed control subjects (n=13)



Symptom scores and lung function during experimental rhinovirus infection

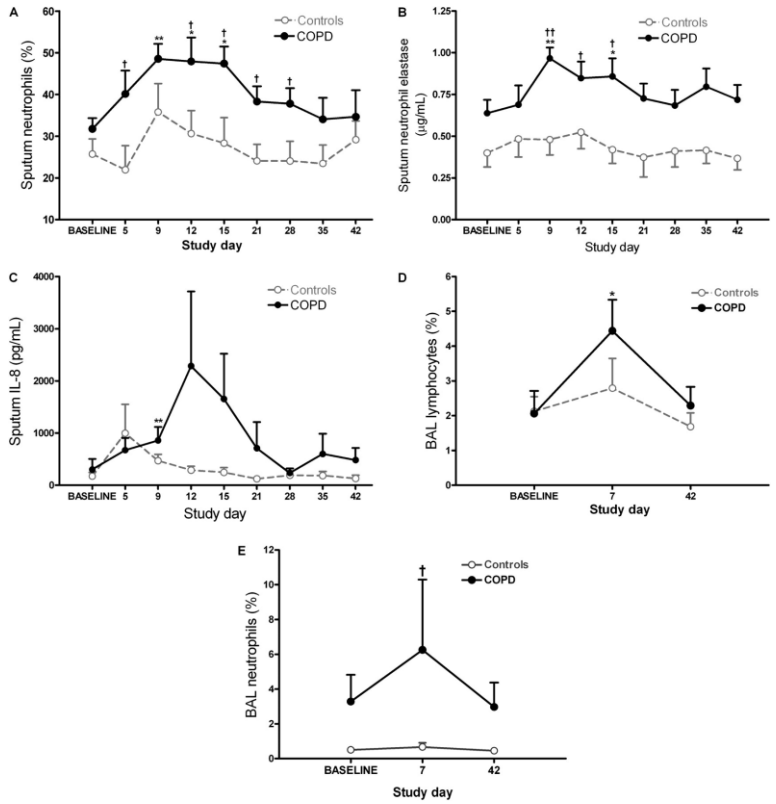


Virus load in nasal lavage and sputum

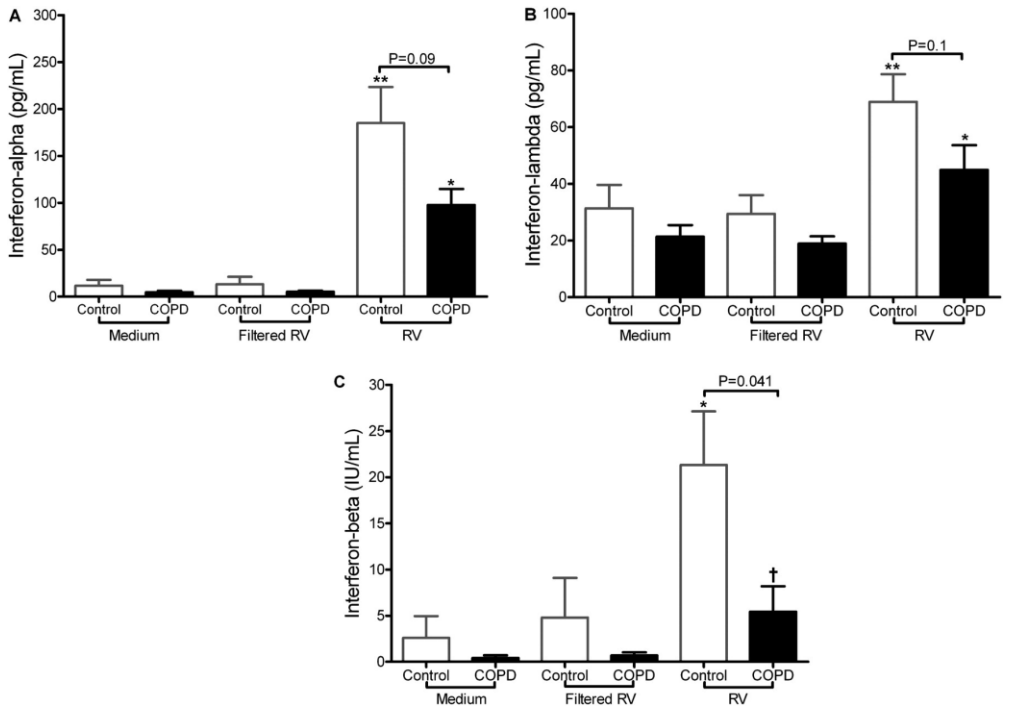
Am J Respir Crit Care Med Vol 183. pp 734–742, 2011

Causal relationship between viral infection and AECOPD

- **Impaired IFN production and neutrophilic inflammation** may be important mechanisms in virus-induced COPD exacerbations.



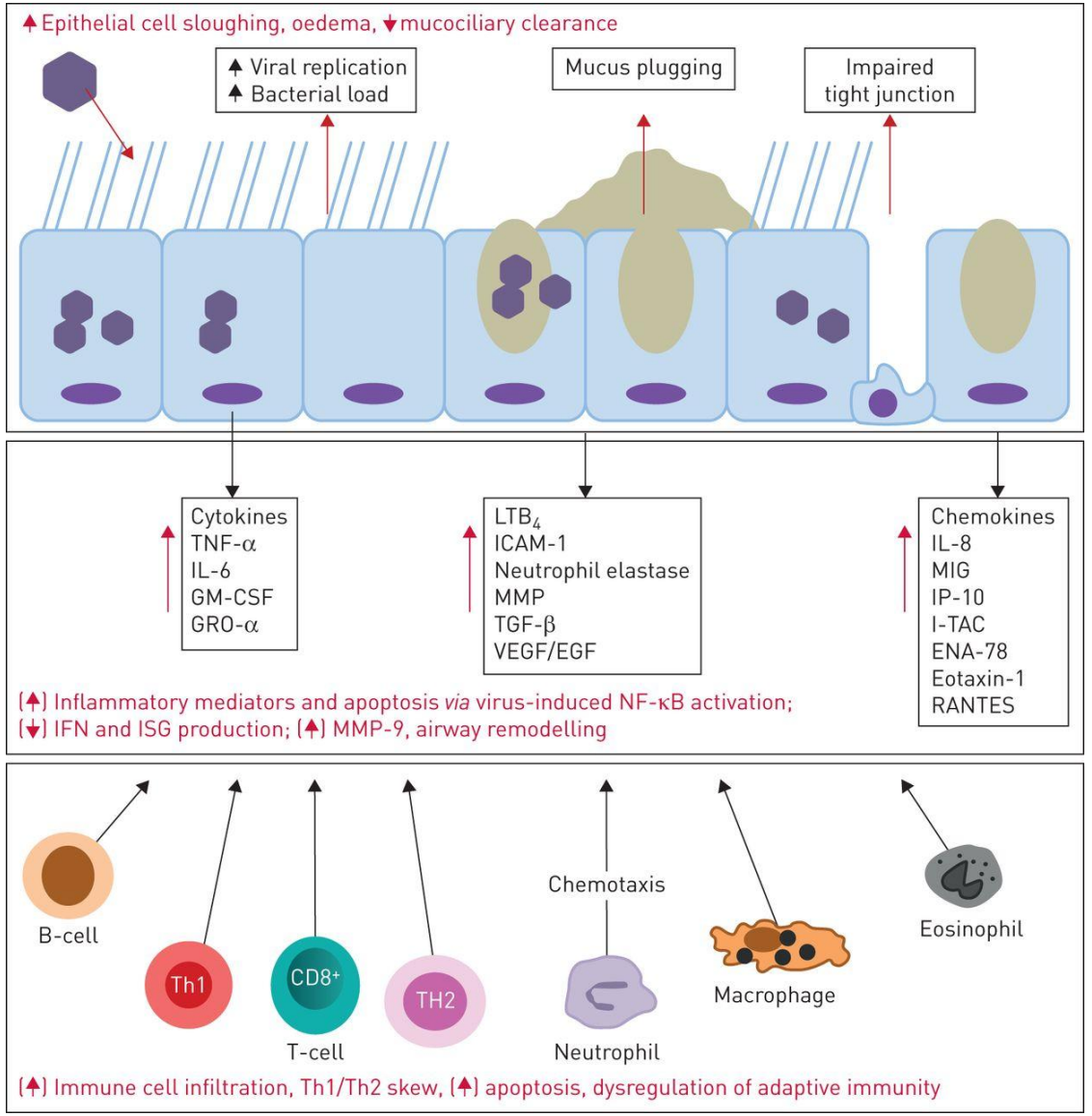
Airway inflammatory cells and soluble mediators during experimental rhino virus infection



Interferon responses in BAL cells

Mechanisms of virus-induced airway inflammation

- HRV → activation of EGFR → release mucin and IL-8
- Expression of **cytokines and chemokines↑**
- Attraction of **various inflammatory cells** (neutrophils, T-cells, macrophages, dendritic cells)
- Preferentially target **airway epithelial cells**
  - epithelial cell sloughing
  - Goblet cell hyperplasia (mucus plug)
  - microvascular dilatation
  - oedema and immune cell infiltration
- → **impaired mucociliary clearance**
- → **susceptibility to bacterial infection↑**



Eur Respir Rev 2019; 28: 180063

Mechanisms of virus-induced airway inflammation

- Impaired antiviral immunity in COPD: **Interferon deficiency**
  - potential mechanism of increased susceptibility to rhinovirus infection, but remains controversial

Table 2. (*Continued*)

Mediator	*In Vitro**	Animal Studies†	Naturally Occurring Infection‡
Type III IFN (λ1/IL-29, λ2/IL-28)	↑ λ1/2 (121) λ1 (123) ↓ λ1 (138) ↔ *Ex vivo* (105)	↓ λ3 (138), (mRNA) (118)	
Type I IFN (α/β)	↓ (*Ex vivo*) (105) Undetectable (121) ↓ β (138)	↑ (120) ↑ [To poly(I:C)] (119) ↓ (117, 118) ↓ β (138)	
Type II IFN (γ)	↔ (121)	↑ (117, 119) ↔ (120) ↓ (138)	↑ (Serum) (89) ↔ (Serum) (87)

- Disease-relevant proinflammatory cytokines by viral infection
  - IL-8 (CXCL8)
  - IL-6
  - chemokine ligand 5 (CCL5/RANTES)
  - TNF-a
  - IFN-g–induced protein (IP-10/CXCL10)
- → **response is greater in patients with COPD compared with healthy controls**

Ann Am Thorac Soc. 2015 Nov;12 Suppl 2:S115-32.

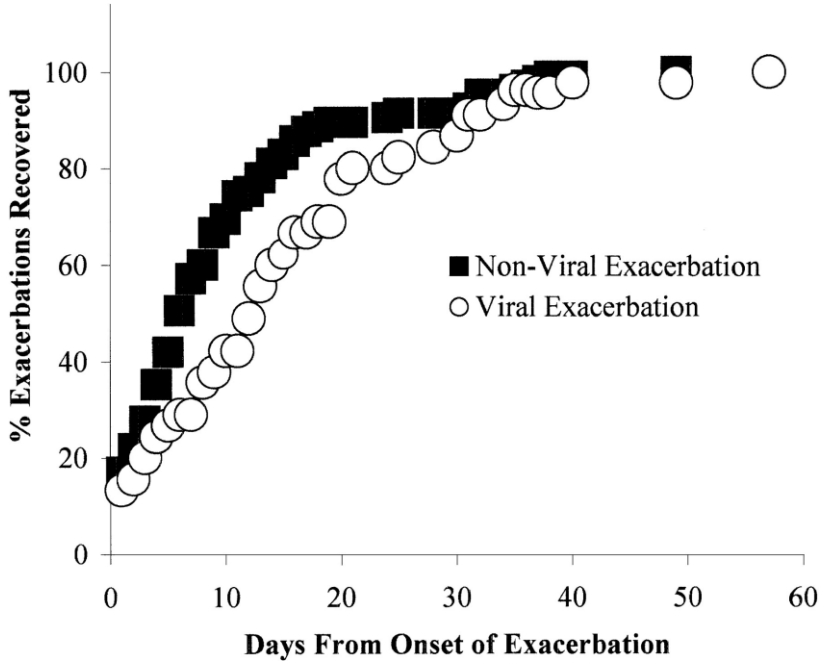
Respiratory viruses in AECOPD

- 83 patients with COPD, 321 exacerbations, 168 nasal aspirates
- Respiratory virus infections: **more severe and frequent exacerbations**

TABLE 3. EFFECT OF SYMPTOMS AT PRESENTATION ON DETECTION OF VIRUSES IN NASAL SAMPLES DURING 168 EXACERBATIONS IN 83 PATIENTS WITH COPD*

Symptom at Presentation	Odds Ratio	p Value
Colds†	3.55	< 0.001
Increased dyspnea and colds†	3.27	0.001
Sore throat	2.27	0.043
Increased sputum volume	1.59	0.182
Increased dyspnea	1.38	0.420
Increased purulent sputum	1.31	0.421
Increased cough	1.22	0.552
Increased wheeze	1.09	0.786

†Colds, Increased nasal congestion and/or increased rhinorrhea.

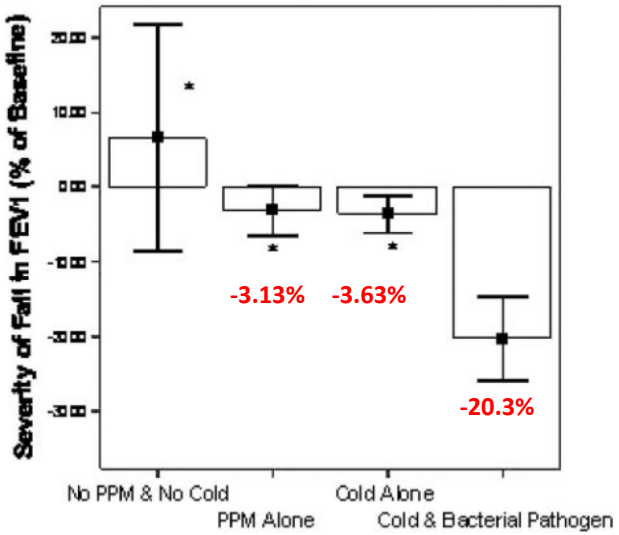


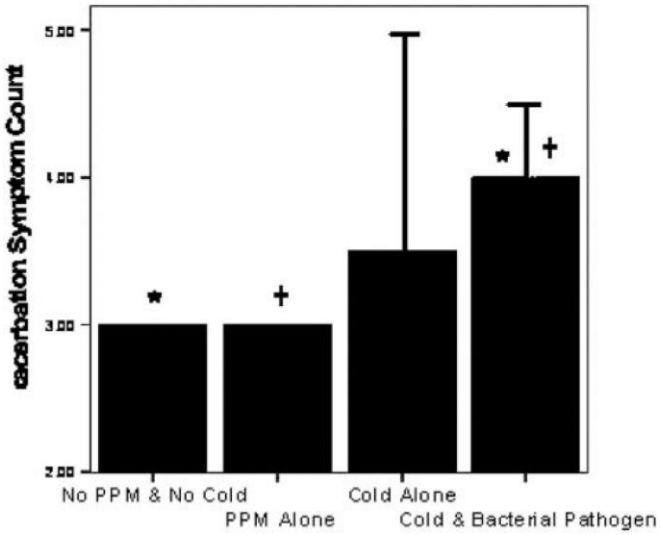
Viral AECOPDs are associated with delayed recovery than colonizer

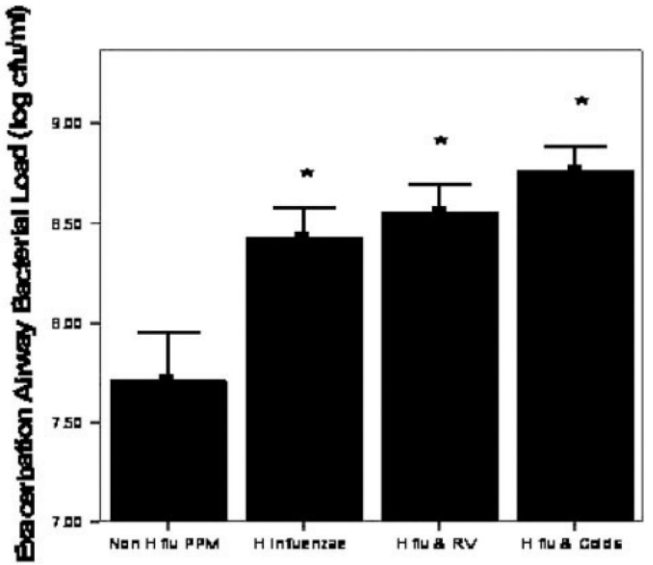
Am J Respir Crit Care Med. 2001 Nov 1;164(9):1618-23.

Interactions between bacterial and viral infection

- COPD (n=39), 56 exacerbations, 69.6% of bacterial pathogen, 19.6% of rhinovirus
- In exacerbations with both **cold symptoms and a bacterial pathogen** vs. **bacterial pathogen alone**
  - **greater fall of FEV1**
  - **higher symptom count**
  - **higher bacterial loads**



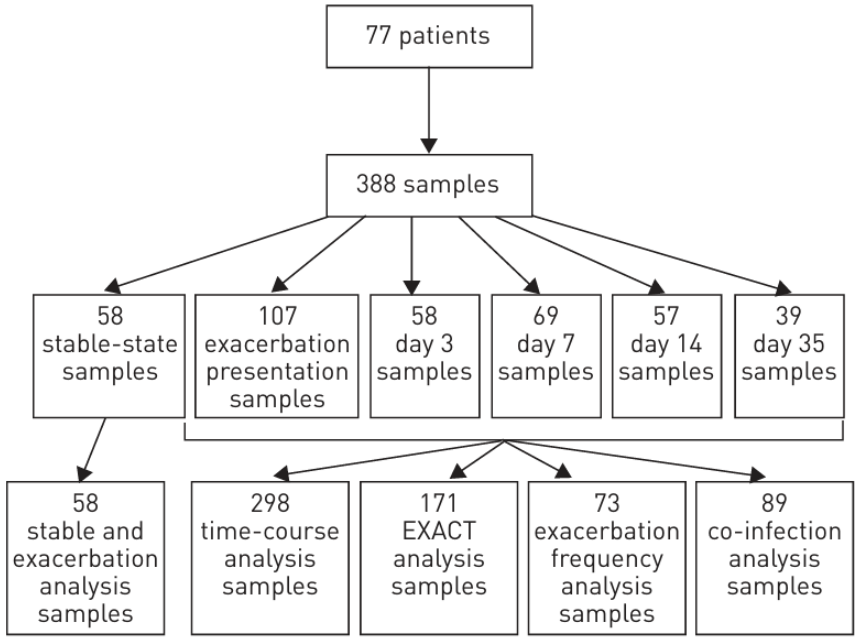




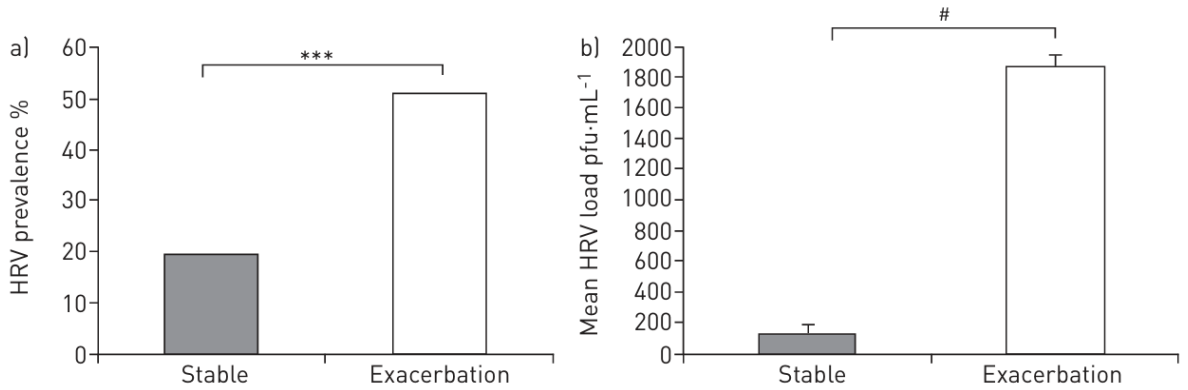
- **Bacterial and viral pathogens** interact to cause additional rises in inflammatory markers and greater exacerbation severity

CHEST 2006; 129:317–324

HRV infection during naturally occurring AECOPD

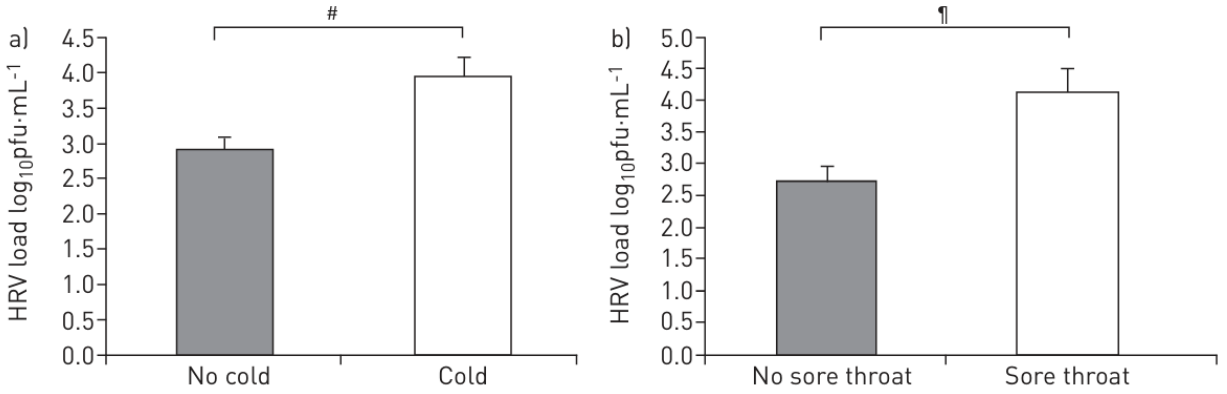


- Higher viral prevalence and load at exacerbation



a) Prevalence of HRV in stable COPD and at exacerbation (53.3% vs. 17.2%, p<0.001)
b) HRV load in stable COPD and at exacerbation

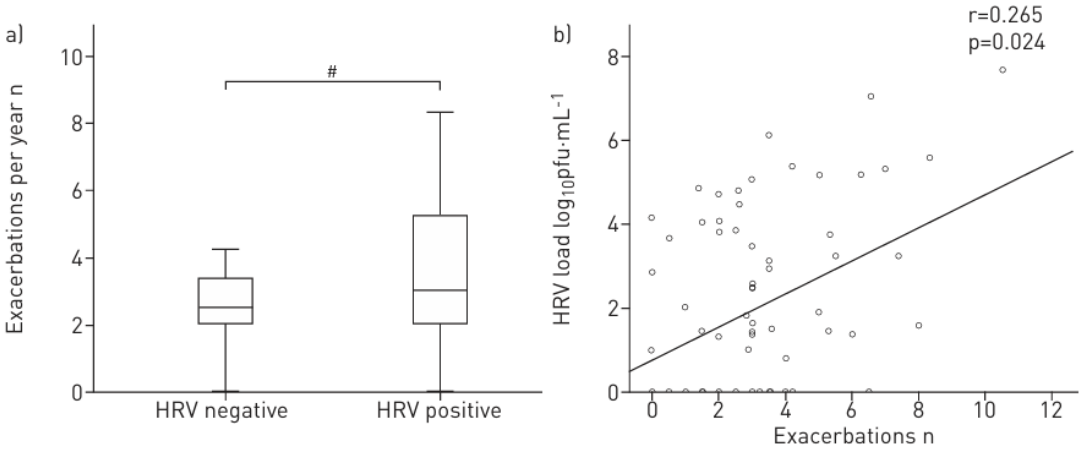
- Higher viral load in patients with cold symptoms or sore throats



Eur Respir J 2014; 44: 87–96

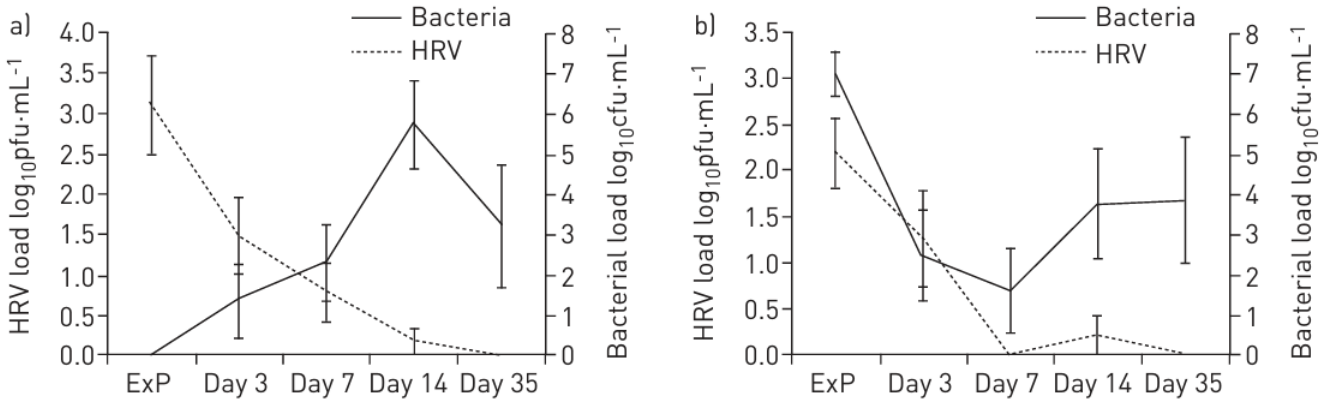
HRV infection during naturally occurring AECOPD

- Frequent exacerbators were more likely to experience HRV infection
- Number of exacerbations per year
  - 3.01 (HRV positive) vs. 2.51 (HRV negative) (p=0.038)



a) Higer number of exacerbations per year in patients with HRV
b) Association between the number of exacerbations per year and the HRV load

- **Secondary bacterial infection is common after HRV infection.**



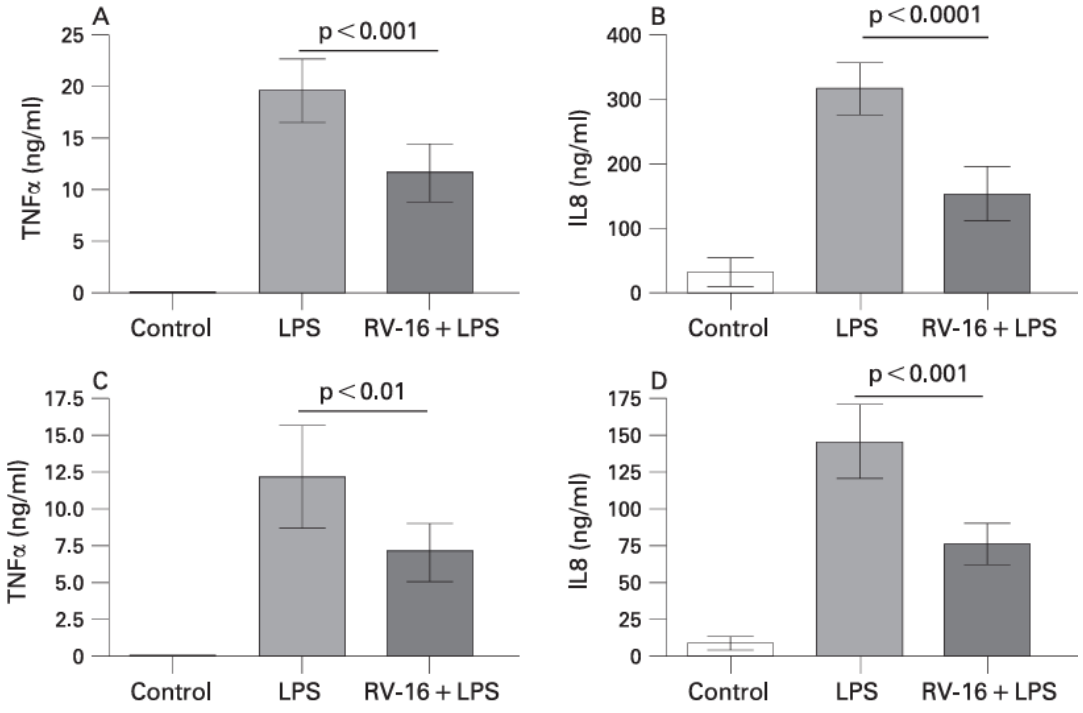
Changes in the load of HRV and typical bacteria during AECOPD and recovery
a) **negative for bacteria at exacerbation (n=11) → 73% (8/11) by day 14**
b) positive for bacteria at exacerbation (n=10)

N Engl J Med 2002;347:465-71.

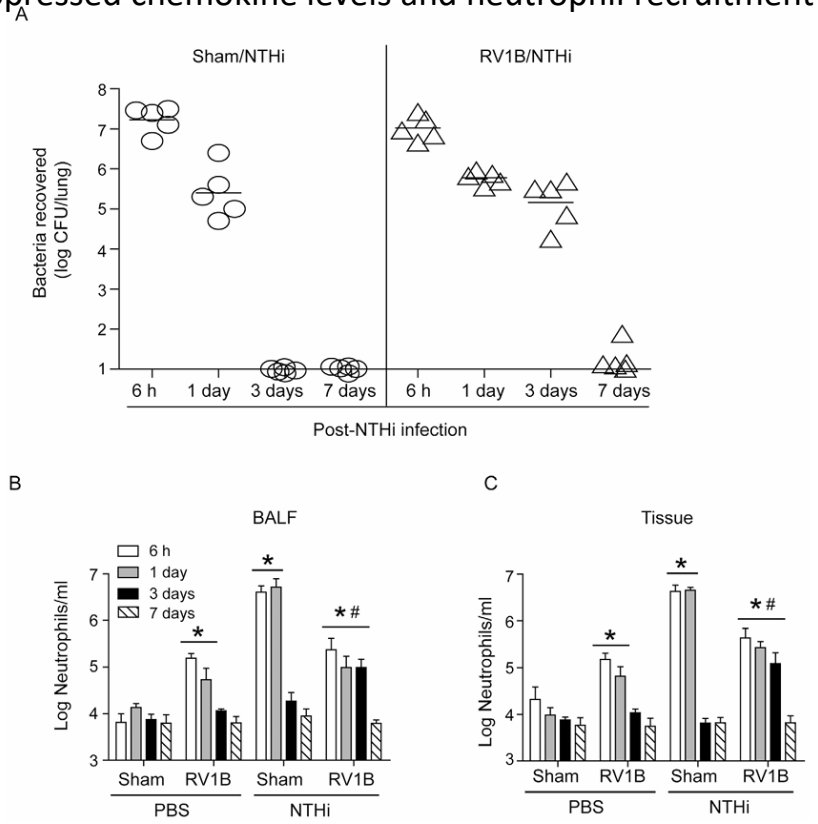
Mechanisms of viral-bacterial coinfection

- **Viral impairment of macrophage response to bacteria**

→ **neutrophil recruitment and bacterial clearance ↓**



- Animal models: effects of RV on subsequent infection with NTHi
- **Delayed bacterial clearance** in RV/NTHi
- → suppressed chemokine levels and neutrophil recruitment



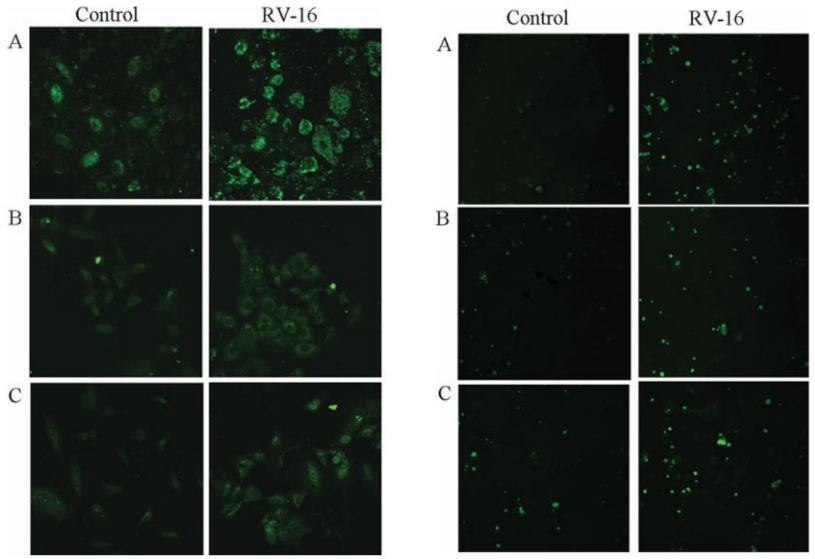
RV infection promotes bacterial persistence and decreases neutrophil infiltration to subsequent bacterial challenge in vivo.

Thorax. 2008 Jun;63(6):519-25.
PLoS Pathog. 2012;8(10):e1002969.

Mechanisms of viral-bacterial coinfection

- **Upregulation of adhesion molecules in the bronchial epithelium**
- RV-16 infection→ expression of fibronectin, platelet-activating factor receptor, carcinoembryonic antigen-related cell adhesion molecule ↑
- Compared with rhinovirus-uninfected control cells, **the adhesion of S. aureus, S. pneumoniae, and H. influenzae increased significantly in rhinovirus-infected nasal epithelial cells.**

(A) Fn
(B) PAR-r
(C) CEACAM



Confocal microscopy of primary human nasal epithelial cells

(A) S. aureus
(B) S. pneumoniae
(C) H. influenzae

TABLE I.
Effects of RV-16 Infection on the mRNA Expression of Cell Adhesion Molecules and Bacterial Adhesions.

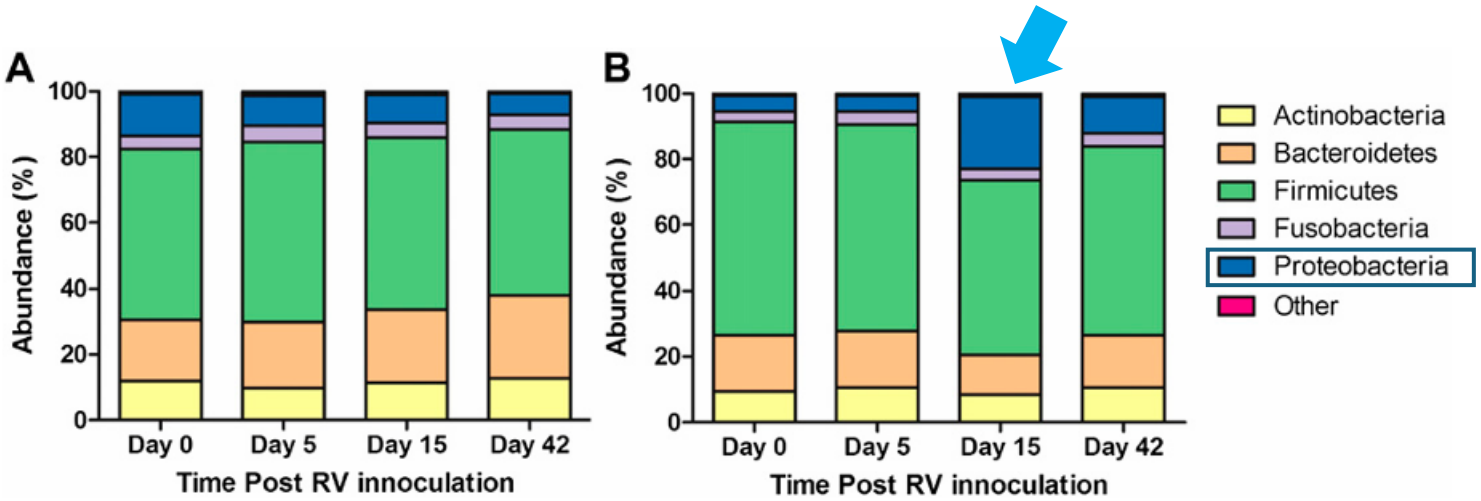
	Cell Adhesion Molecules (mRNA)			Bacterial Adhesions		
Fold increase over control	Fn	PAR-r	CEACAM	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Hemophilus influenzae*
Median (Range)	1.68* (1.67–1.68)	1.52* (1.51–1.52)	1.51* (1.50–1.51)	2.53* (2.45–2.57)	1.51* (1.47–1.77)	2.74* (2.41–2.76)

*$P < .05$.
Fn = fibronectin; PAF-r = platelet-activating factor receptor; CEACAM = carcinoembryonic antigen-related cell adhesion molecule.

Laryngoscope. 2009 Jul;119(7):1406-11.

Bacterial airway microbiome after rhinovirus AECOPD

- In the subjects with COPD
  - ↑ **proteobacterial** sequences on Day 15 after rhinovirus infection
  - ↓ Firmicutes and Bacteroidetes phyla



Distribution of bacterial phyla at each time point after rhinovirus inoculation.
(A) In the control subjects
(B) In subjects with COPD

- Within the Proteobacteria phylum
  - **21% increase in the relative abundance of a Haemophilus species**
  - 9.5% rise in the relative abundance of Neisseriaceae

- **Rhinovirus infection in COPD alters the respiratory microbiome and may precipitate secondary bacterial infections**

N Engl J Med 2002;347:465-71.

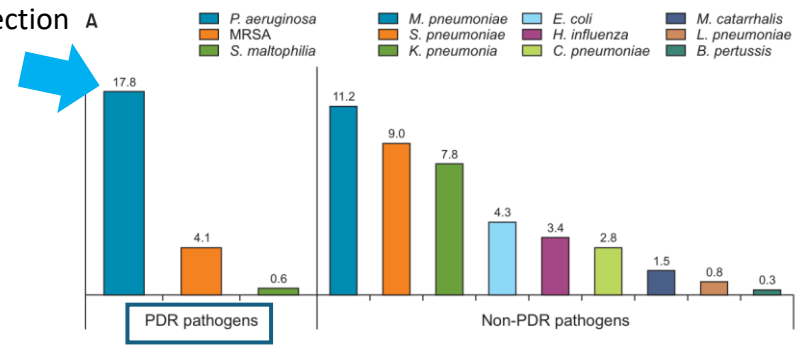
Clinical significance of pathogens during AECOPD

- 1,186 AECOPD at 28 hospitals in South Korea, 2015 ~ 2018
- Bacteria 22.1%, viruses 22.5%, both 10.9%
- **P. aeruginosa 17.8%,** M. pneumoniae 11.2%, S. pneumoniae 9.0%, influenza A virus 19.0%, rhinovirus 15.8%, RSV 6.4%

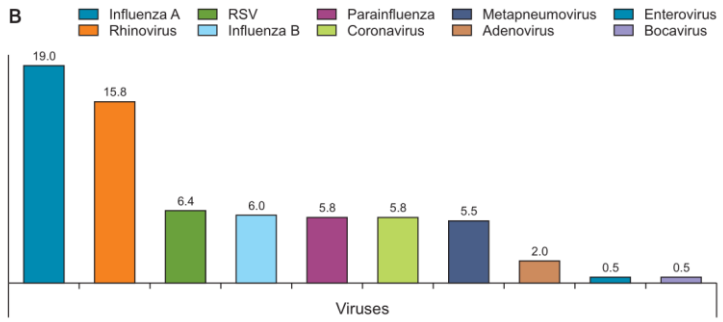
Table 1. Baseline characteristics of patients

Characteristic	Total (n=1,186)
Age, yr	78.8±9.2
Male sex	979 (82.5)
Duration of COPD, yr	7.6±6.6
Smoking history	
Never smoked	313 (27.1)
Current smoker	156 (13.5)
Former smoker	688 (59.5)
Pack year	38.7±26.0
Underlying respiratory disease	
Tuberculosis	377 (31.8)
Bronchiectasis	169 (14.2)
Interstitial lung disease	27 (2.3)
Comorbidities	
Diabetes mellitus	318 (26.8)
Hypertension	584 (49.2)
Liver cirrhosis	23 (1.9)
Congestive heart failure	166 (14.0)
Chronic kidney disease	76 (6.4)
Cerebrovascular disease	70 (5.9)
Advanced cancer	138 (11.6)
FEV_1, %	49.5±21.1
CAT score	22.5±9.8
mMRC	2.3±0.9
During AECOPD	
ICU administration	112 (9.5)
Hospital length of stay, day	12.6±13.7
Antibiotics use	
Unused	47 (4.2)
Monotherapy	282 (25.5)
Beta-lactam	163 (57.8)
Quinolone	107 (37.9)
Macrolide	5 (1.8)
Others	7 (2.5)
Dual combination	651 (58.8)
Beta-lactam+Quinolone	280 (43.0)
Beta-lactam+Macrolide	236 (36.3)
Beta-lactam+Others	31 (4.8)
Quinolone+Others	27 (4.1)
Macrolide+Others	19 (2.9)
Triple combination	128 (11.5)
Levels of healthcare system	
Secondary	396 (33.5)
Tertiary	709 (66.5)

Bacterial infection



Viral infection



Tuberc Respir Dis (Seoul). 2025 Apr;88(2):292-302.

Clinical significance of pathogens during AECOPD

- Potentially drug-resistant (PDR): **P. aeruginosa, MRSA, and S. maltophilia**
- PDR pathogens: **hospital stays (15.9 days vs. 12.4 days, p=0.018)↑, ICU admission (15.9% vs. 9.5%, p=0.030)↑**

Table 2. Baseline characteristics and clinical features of patients during AECOPD according to PDR pathogen identification

Characteristic	Non-PDR pathogens (n=511)	PDR pathogens (n=142)	p-value
Length of hospitalization, day	12.4±14.7	15.9±17.3	0.018
Length of exacerbation, day	12.2±7.9	13.3±9.8	0.185
ICU admission	47 (9.5)	22 (15.9)	0.030
Duration of steroid use, day	12.8±14.9	19.7±44.2	0.107
Antibiotic use			
Monotherapy			
Beta-lactam	383 (80.0)	112 (81.8)	0.641
Quinolone	220 (45.9)	70 (51.1)	0.285
Macrolide	150 (31.3)	29 (21.2)	0.021
Other	23 (4.8)	17 (12.4)	0.001
Dual combination			
Beta-lactam+Quinolone	117 (24.4)	36 (26.3)	0.658
Beta-lactam+Macrolide	122 (25.5)	24 (17.5)	0.054
Triple combination	52 (10.9)	21 (15.3)	0.153

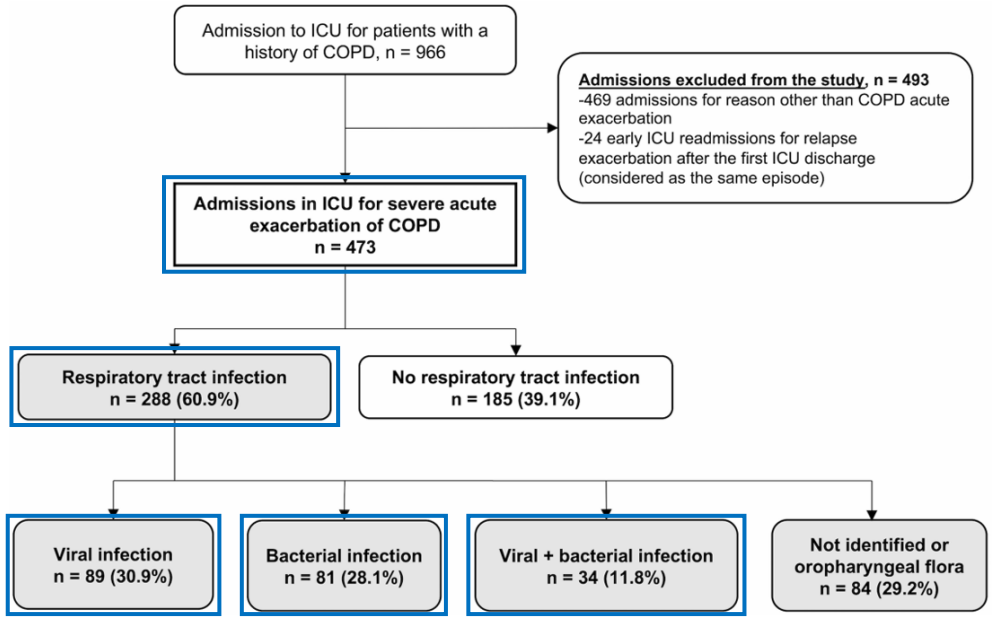
Table 3. Multivariate logistic analysis of the associated factors for infection with PDR pathogens during AECOPD

Associated factors	ICS model		Triple inhaler model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, yr	1.01 (0.98–1.03)	0.638	1.01 (0.98–1.04)	0.573
Male sex	1.41 (0.78–2.55)	0.261	1.50 (0.82–2.74)	0.189
BMI, kg/m^2	0.97 (0.91–1.04)	0.405	0.97 (0.91–1.04)	0.355
FEV_1 >60%	0.74 (0.41–1.34)	0.319	0.79 (0.44–1.43)	0.435
Comorbidities				
Tuberculosis	1.66 (1.01–2.75)	0.046	1.64 (0.99–2.72)	0.054
Bronchiectasis	1.99 (1.06–3.75)	0.032	1.94 (1.02–3.67)	0.043
Treatment status				
Systemic steroids	1.47 (0.85–2.57)	0.172	1.45 (0.84–2.53)	0.186
ICS	1.62 (0.97–2.71)	0.066	NA	NA
Triple therapy	NA	NA	2.04 (1.24–3.35)	0.005

PDR: potentially drug-resistant; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; OR: odds ratio; CI: confidence interval; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; NA: not applicable.

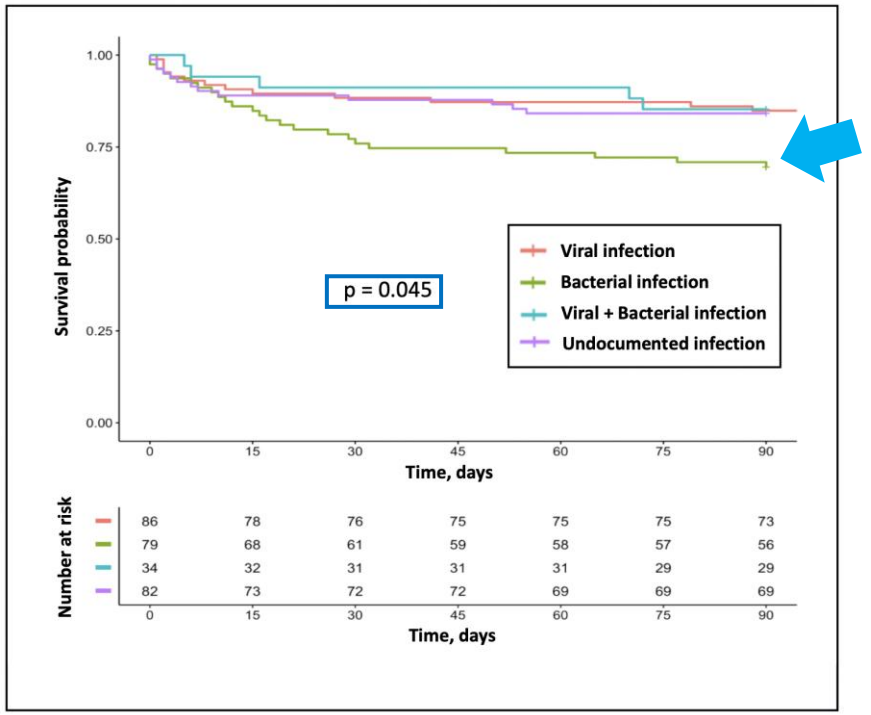
Respiratory infections during AECOPD in the ICU

- Single-centre cohort study, 2015–2021, ICU for severe AECOPD
- Bacterial cause: 39.9%



IMV: 139 (29.4%)
ICU mortality: 47 (9.9%)
Hospital mortality: 67 (14.2%)

Risk factors associated with in-hospital mortality		
Age, years (+1 year)	**1.03 (1.01–1.06)**	**0.03**
Immunodeficiency	**1.96 (1.08–3.55)**	**0.02**
Performance status (−1 point)	**1.78 (1.23–2.57)**	**0.002**
Bacterial infection	1.71 (0.92–3.18)	0.08
Corticosteroids use during ICU stay	**0.53 (0.29–0.98)**	**0.04**

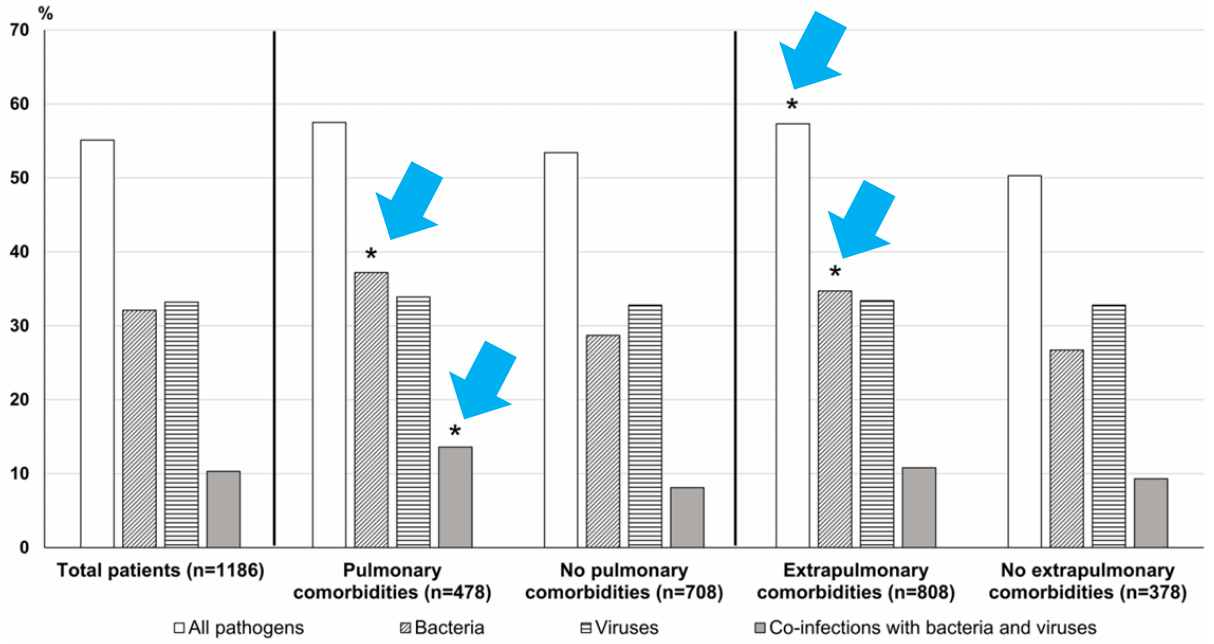


KM survival curves at 90 days according to the type of respiratory infection

Int J Chron Obstruct Pulmon Dis. 2024 Feb 27;19:555-565.

Comorbidities and microbiologic findings

- 1,186 AECOPD at 28 hospitals in South Korea, 2015 ~ 2018
- Causative pathogens 55.1%, bacteria 32.1%, viruses 33.2%, co-infections 10.3%
- **Bacterial** infections and co-infections: more prevalent **pulmonary comorbidities**
- **Bacterial** pathogens: higher rate of **extrapulmonary comorbidities**



Int J Chron Obstruct Pulmon Dis. 2022 Apr 20;17:855-867.

Comorbidities and microbiologic findings

- **As the number of comorbidities increased, the risk of bacterial infection increased considerably**.

Table 3 The Multivariate Adjusted Odds Ratios for Identification of Respiratory Pathogens According to the Number of Comorbidities

	All Pathogens		Bacteria		Viruses		Bacterial and Viral Co-Infection	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Age	1.008 (0.995–1.021)	0.216	1.004 (0.991–1.018)	0.558	1.006 (0.993–1.020)	0.371	1.003 (0.982–1.024)	0.795
Male sex	0.693 (0.508–0.945)	0.020	0.757 (0.552–1.038)	0.084	0.809 (0.591–1.109)	0.188	0.824 (0.515–1.320)	0.421
Use of ICS	1.240 (0.984–1.562)	0.068	1.484 (1.159–1.900)	0.002	0.901 (0.706–1.149)	0.400	1.102 (0.756–1.606)	0.612
Number of comorbidities								
0	Reference		Reference		Reference		Reference	
1–2	1.456 (1.073–1.975)	0.016	1.430 (1.008–2.027)	0.045	1.461 (1.049–2.035)	0.025	2.239 (1.197–4.189)	0.012
≥ 3	1.514 (1.052–2.177)	0.025	2.101 (1.409–3.132)	<0.001	1.025 (0.688–1.527)	0.904	2.195 (1.092–4.413)	0.027

- **AECOPD patients with comorbidities** were more likely to experience infection-related exacerbations compared to those without comorbidities.

Int J Chron Obstruct Pulmon Dis. 2022 Apr 20;17:855-867.

P. aeruginosa in AECOPD

- 736 cases of AECOPD, Korea University Guro Hospital, 2011 ~ 2017
- P. aeruginosa
  - frequently identified in severe and very severe COPD patients
  - associated with in-hospital mortality

Table 2. Bacterial and Viral Pathogen Identification according to GOLD Stage

	All events (n=736)	GOLD I (n=57)	GOLD II (n=281)	GOLD III (n=307)	GOLD IV (n=91)	*p* value
Only bacterial identification	200 (27.2)	11 (19.3)	68 (24.2)	91 (29.6)	30 (33.0)	0.020
Only viral identification	159 (21.6)	16 (28.1)	68 (24.2)	60 (19.5)	15 (16.5)	0.031
Bacterial-viral co-identification	107 (14.5)	4 (7.0)	37 (13.2)	53 (17.3)	13 (14.3)	0.112
No identification	270 (36.7)	26 (45.6)	108 (38.4)	103 (33.6)	33 (36.3)	0.141
Pseudomonas aeruginosa	96 (13.0)	4 (7.0)	29 (10.3)	47 (15.3)	16 (17.6)	0.011
Streptococcus pneumoniae	84 (11.4)	3 (5.3)	29 (10.3)	38 (12.4)	14 (15.4)	0.048
Haemophilus influenzae	39 (5.3)	5 (8.8)	15 (5.3)	17 (5.5)	2 (2.2)	0.158
Staphylococcus aureus	35 (4.8)	1 (1.8)	16 (5.7)	10 (3.3)	8 (8.8)	0.333
Klebsiella pneumoniae	20 (2.7)	1 (1.8)	10 (3.6)	8 (2.6)	1 (1.1)	0.509
Influenza virus	91 (12.4)	8 (14.0)	42 (14.9)	32 (10.4)	9 (9.9)	0.112
Rhinovirus	69 (9.4)	5 (8.8)	21 (7.5)	35 (11.4)	8 (8.8)	0.387
Parainfluenza virus	38 (5.2)	2 (3.5)	13 (4.6)	15 (4.9)	8 (8.8)	0.165
Metapneumovirus	36 (4.9)	3 (5.3)	14 (5.0)	15 (4.9)	4 (4.4)	0.832

Table 3. Bacterial and Viral Pathogen Identification according to In-hospital Mortality

	All events (n = 736)	Mortality events in hospital (n=32)	Non-mortality events in hospital (n=704)	*p* value
Only bacterial identification	200 (27.2)	15 (46.9)	185 (26.3)	0.010
Only viral identification	159 (21.6)	1 (3.1)	158 (22.4)	0.009
Bacterial-viral co-identification	107 (14.5)	8 (25.0)	99 (14.1)	0.118
No identification	270 (36.7)	8 (25.0)	262 (37.2)	0.161
Pseudomonas aeruginosa	96 (13.0)	8 (25.0)	88 (12.5)	0.056
Streptococcus pneumoniae	84 (11.4)	2 (6.3)	82 (11.6)	0.567
Haemophilus influenzae	39 (5.3)	2 (6.3)	37 (5.3)	0.684
Staphylococcus aureus	35 (4.8)	6 (18.8)	29 (4.12)	0.003
Klebsiella pneumoniae	20 (2.7)	4 (12.5)	16 (2.27)	0.009
Influenza virus	91 (12.4)	3 (9.4)	88 (12.5)	0.787
Rhinovirus	69 (9.4)	4 (12.5)	65 (9.2)	0.530
Parainfluenza virus	38 (5.2)	1 (3.1)	37 (5.3)	1.000
Metapneumovirus	36 (4.9)	0 (0.0)	36 (5.1)	0.396

Yonsei Med J 2019 Feb;60(2):216-222

P. aeruginosa in hospitalized AECOPD

- 494 AECOPD admission, National Taiwan University Hospital, 2000 ~ 2004

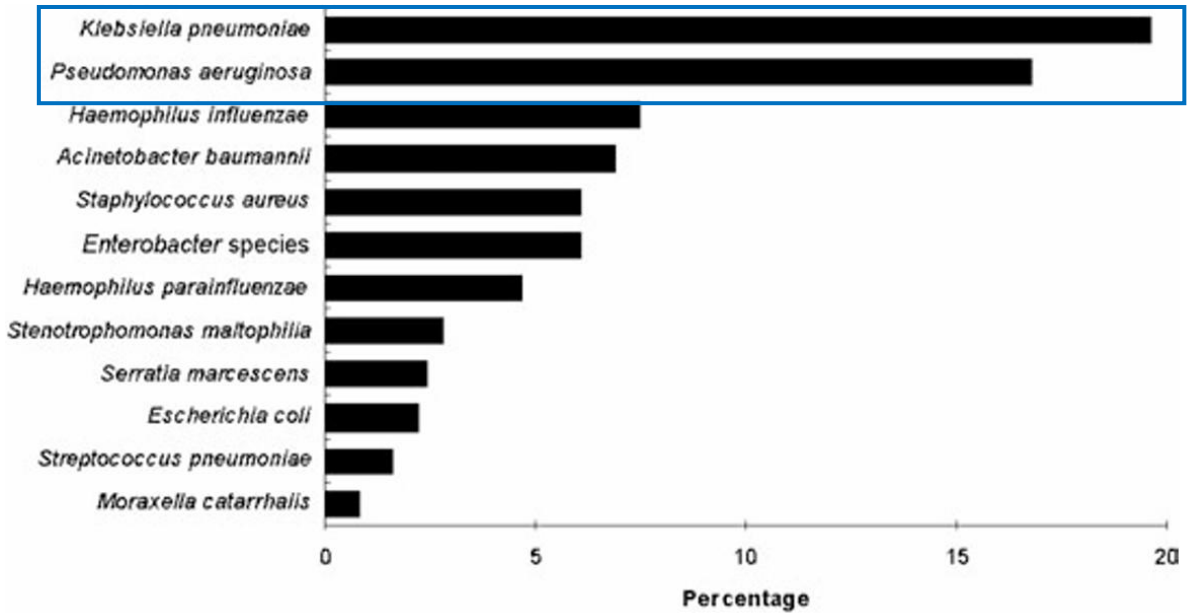
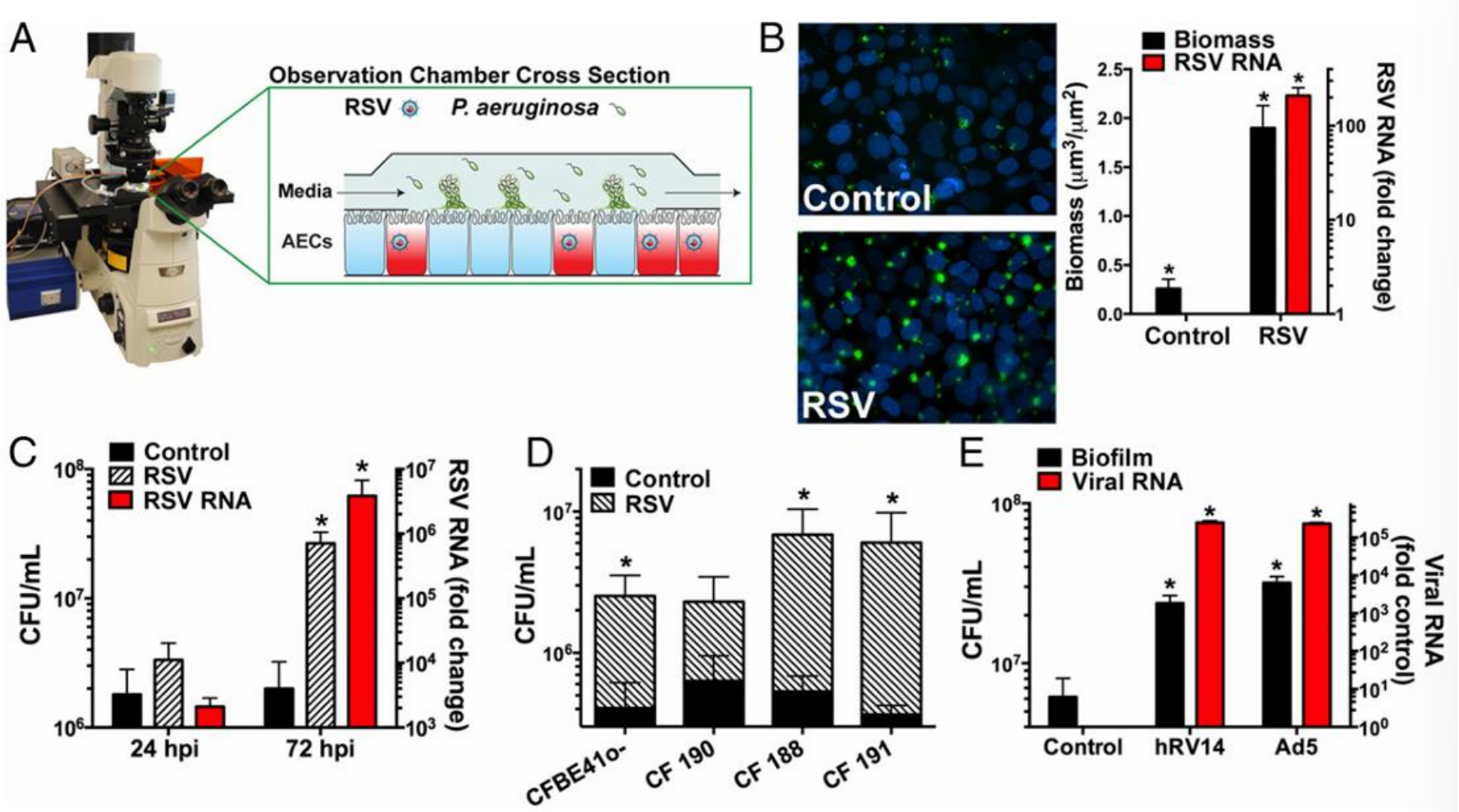


Table 4 Independent risk factors for adverse in-hospital outcomes

Independent risk factors for outcomes	Odds ratio (95% CI)	*P*-value
Hospital stay >14 days		
Pseudomonas aeruginosa	2.31 (1.41–3.81)	0.001
Enterobacter species	2.24 (1.02–4.94)	0.045
Mixed flora	1.72 (1.02–2.90)	0.04
FEV_1% predicted*†	0.99 (0.97–1.00)	0.048
Endotracheal intubation		
Escherichia coli	4.73 (1.4–15.87)	0.012
Pseudomonas aeruginosa	1.80 (1.06–3.03)	0.029
Death		
Endotracheal intubation	14.81 (5.08–43.12)	<0.001
Pseudomonas aeruginosa	3.19 (1.21–8.38)	0.019
Age (year)†	1.10 (1.03–1.17)	0.003

Respirology (2007) 12, 81–87

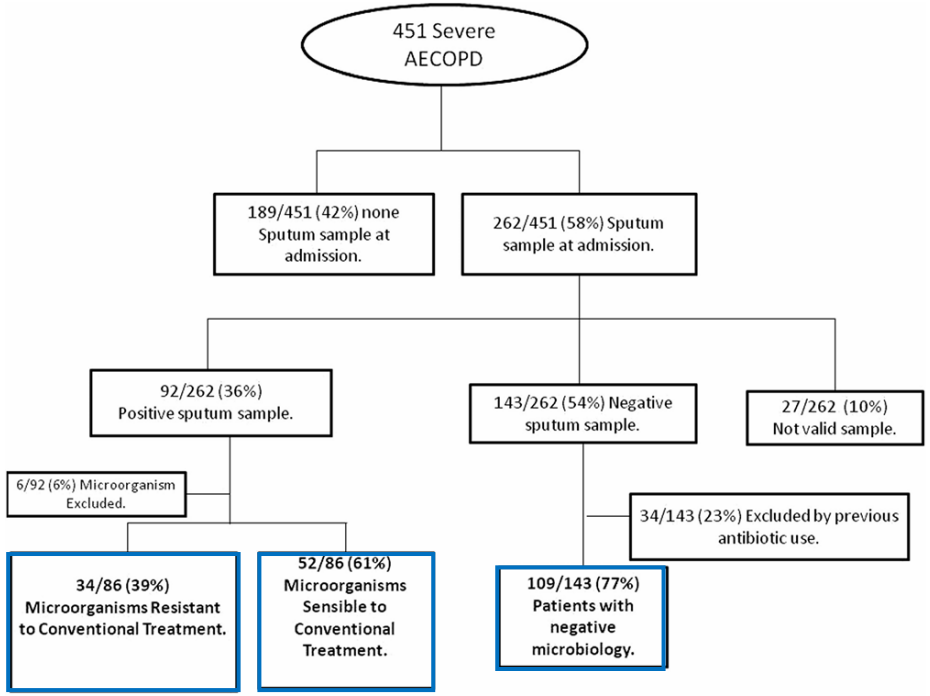
Molecular mechanisms of AECOPD with P. aeruginosa

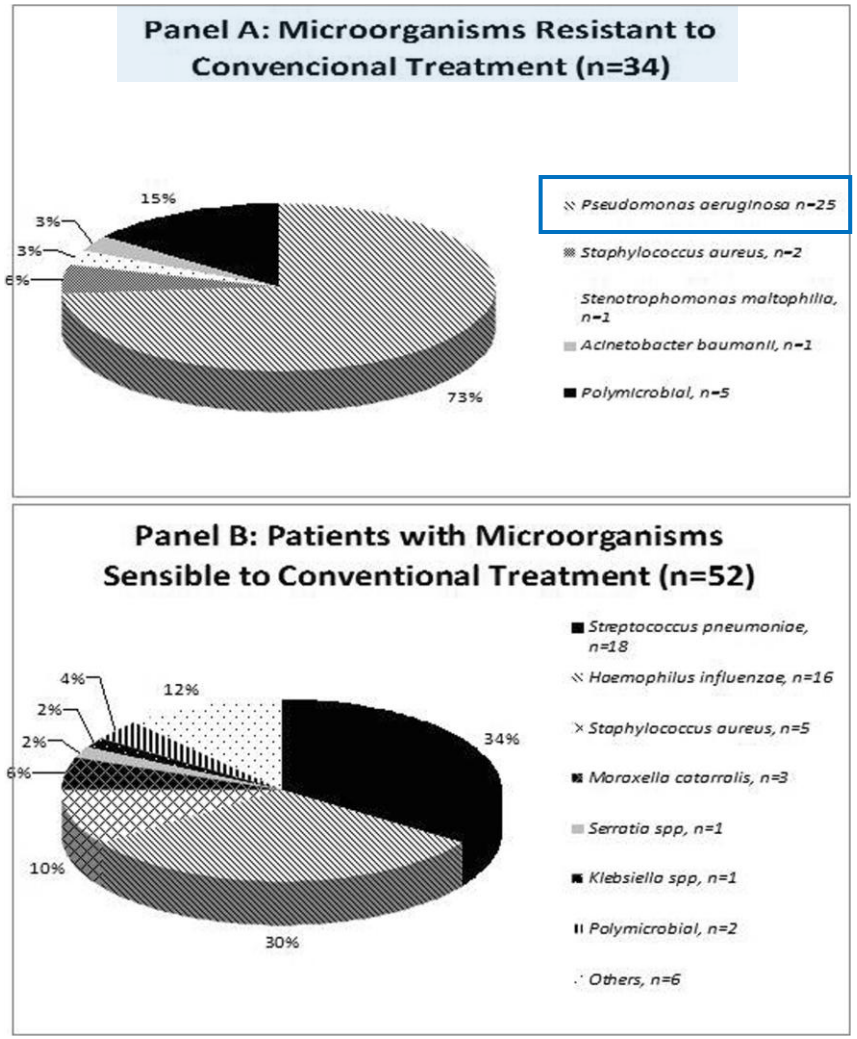


Proc Natl Acad Sci U S A. 2016 Feb 9;113(6):1642-7.

Microorganisms resistant to conventional antimicrobials

- Severe AECOPD (hospitalized), 2009 ~ 2015





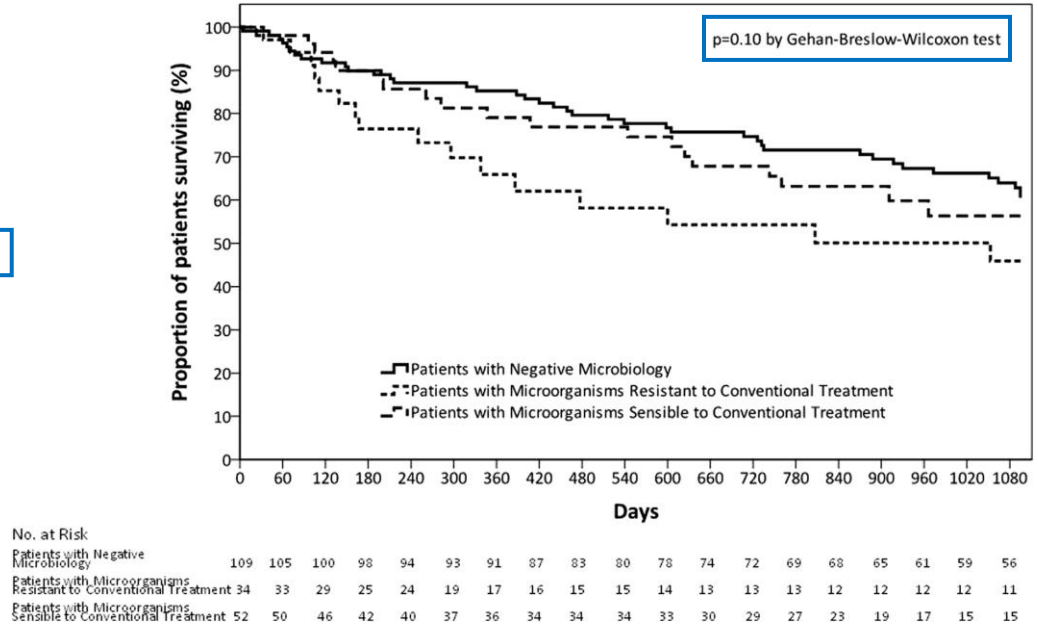
Respir Res. 2018 Jun 15;19(1):119.

Microorganisms resistant to conventional antimicrobials

- Mortality rates were comparable at 30-days, one year and 3 years
- **Longer hospital stays in patients with MDRO**

Table 3 Clinical outcomes

	Patients with microorganisms resistant to conventional treatment ($n = 34$)	Patients with microorganisms sensitive to conventional treatment ($n = 52$)	Patients with negative microbiology ($n = 109$)	*P* value
AECOPD after 30 days of discharge, n (%)	24 (73)	21 (47)	57 (56)	0.070
Number of AECOPD after 30 days of discharge, median (IQR)	1 (0; 3)	0 (0; 2)	1 (0; 1)	0.075
Time to the next AECOPD, median (IQR), days	39 (19; 170)	52 (27; 166)	86 (26; 182)	0.577
Length of stay, median (IQR), days	9 (7; 14)[c]	8 (6; 10.5)	8 (6; 10)[a]	**0.026**
ICU admission, n (%)	4 (12)	6 (12)	12 (11)	0.981
IMV, n (%)	2 (6)	1 (2)	3 (2)	0.564
NIMV, n (%)	6 (18)	10 (19)	16 (15)	0.780
30-day mortality, n (%)	1 (3)	1 (2)	4 (4)	0.834
1-year mortality, n (%)	11 (32)	12 (23)	19 (17)	0.173
3-years mortality, n (%)	16 (59)	19 (56)	40 (43)	0.211



MDR bacteria in patients with severe AECOPD

- **ICU admitted AECOPD and MV for >48 hr** (n=857), 1996 ~ 2001
- MDR bacteria: MRSA, CRPA, A. baumannii, S. maltophilia, ESBL–producing GNB
- **MDR: 69 (8%), no MDR bacteria: 191 (22%), no bacteria: 597 (69%)**

Table 3. Risk factors for multiple-drug-resistant (MDR) bacteria in multivariate analyses

	All Study Patients (n = 857)		Patients with Positive Tracheal Aspirate (n = 260)		Patients with MDR Bacteria and Patients with No Bacteria (n = 666)	
Risk Factors	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)
Previous antibiotic treatment	.013	2.4 (1.2–4.7)	.014	2.4 (1.1–5)	.045	1.9 (1–3.9)
Previous endotracheal intubation	<.001	31 (12–82)	<.001	33 (12–86)	<.001	32 (11–84)

Table 4. Characteristics of study patients during intensive care unit (ICU) stay and outcomes

	MDR Bacteria (n = 69)	No MDR Bacteria (n = 788)	p^a	Bacteria Other Than MDR (n = 191)	p^a	No Bacteria (n = 597)	p^a
Ventilator-associated pneumonia	16 (23)	47 (5)	<.001[b]	10 (5)	<.001[b]	37 (6)	<.001[b]/.165
Duration of antibiotic treatment, days	9 ± 7	7 ± 6	.010	8 ± 6	.511	6 ± 5	<.001/<.001
Corticosteroid use	38 (55)	382 (48)	.183	107 (56)	.471	275 (46)	.011[b]/.344
Duration of mechanical ventilation, days	13 ± 12	9 ± 10	<.001	10 ± 11	.046	7 ± 9	<.001/<.001
Length of ICU stay, days	18 ± 14	14 ± 13	<.001	15 ± 14	.048	12 ± 11	<.001/<.001
ICU mortality	31 (44)	204 (25)	.001[b]	58 (30)	.022[b]	146 (24)	<.001[b]/.066

Risk factors for MDR bacteria

Table 7. Risk factors for mortality in multivariate analyses

	All Study Patients (n = 857)		Patients with Positive Tracheal Aspirate (n = 260)		Patients with MDR Bacteria and Patients with No Bacteria (n = 666)	
Risk Factors	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)
Number of organ failures	<.001	3.3 (2.5–4.3)	<.001	2.8 (1.6–4.9)	<.001	3.6 (2.6–4.9)
Ventilator-associated pneumonia	<.001	2.9 (1.7–4.8)	—	—	<.001	3.7 (2.8–4.3)
Transfer to the ICU from a ward	.019	1.9 (1.1–3.2)	—	—	—	—
Inappropriate initial antibiotic treatment	—	—	.003	7.1 (1.9–30)	—	—

Crit Care Med 2006; 34:2959–2966

Mortality of COPD Patients with MDR P. aeruginosa

- Hospitalized AECOPD, 2000–2005
- **MDRP**: **absence of susceptibility to three or more antibiotic families** (beta-lactams, quinolones, carbapenems and aminoglycosides)

Table 1
General characteristics of patients with COPD and acute exacerbation (comparison of case-patients and controls).

	With MDRP (n = 50)	Without MDRP (n = 50)	p-value
Age (years) (x ± SD)	69 ± 10	73 ± 7	0.07
Male gender (N, %)	42 (84)	42 (84)	1
FEV_1, % pred. (x ± SD)	33 ± 11	31 ± 13	0.4
Number of admissions, prior to inclusion median (range)	4.5 (0–17)	4 (0–15)	0.07
Number of admissions after inclusion, median (range)	4 (0–16)	2.9 (0–20)	0.03

Table 2
Multiple logistic regression analysis of factors associated with mortality.

	OR	95% CI	p-value
MDPR isolation	6.2	1.7–22.1	0.005
Age (years)	0.9	0.9–1	0.8
FEV_1 (% pred.)	1.05	0.99–1.11	0.09
Previous admissions (n)	0.9	0.8–1	0.1

- Overall crude mortality of patients (p = 0.01)
  - With MDRP: 12% at 1 month, 32% at 1 year, 60% at 2 years
  - Without MDRP: 8% at 1 month, 18% at 1 year, 28% at 2 years

- In hospitalized AECOPD patients, acute exacerbation with **MDRP** in sputum was associated with **higher mortality**.

Infection. 2009 Feb;37(1):16-9.

Routine use of antipseudomonal antibiotic

- 437 ICU patients with AECOPD (retrospective), 2009 ~ 2017
- Antibiotics active against P. aeruginosa (**PAA**): 271 patients (62%)
  - Piperacillin/Tazobactam(81%), Meropenem(9%), Ciprofloxacin(6%), Ceftazidime(4%)
- Antibiotics with no antipseudomonal activity (**PAI**): 166 patients (38%)
  - Ampicillin/Sulbactam (80%), Ceftriaxone (11%) Moxifloxacin (9%)

Table 1
Characteristics of the treatment groups at admission and follow up parameters.

Variable	Population $n = 437$ (100%)	PAI $n = 166$ (38%)	PAA $n = 271$ (62%)	p-value
Age[a]	68 (10)	(12)	68 (9)	0.251[b]
Sex				
Female[c]	203 (46.5)	82 (49.4)	121 (44.6)	0.334[d]
COPD grade				
GOLD II[c]	12 (2.7)	5 (3)	7 (2.6)	0.790[d]
GOLD III[c]	40 (9.2)	12 (7.2)	28 (10.3)	0.275[d]
GOLD IV[c]	140 (32)	37 (22.3)	103 (38)	0.001[d]
Grade unknown[c]	245 (56.1)	112 (67.5)	133 (49.1)	<0.001[d]
Comorbidities				
Diabetes mellitus[c]	143 (32.7)	49 (29.5)	94 (34.7)	0.264[d]
Arterial hypertension[c]	282 (64.5)	103 (62)	179 (66.1)	0.396[d]
CHD[c]	142 (32.5)	50 (30.1)	92 (33.9)	0.407[d]
CHF[c]	94 (21.5)	37 (22.3)	57 (21)	0.756[d]
GFR[e]	62 (41–85)	62 (46–87)	63 (40–84)	0.427[f]
Pretreatment				
Prednisone[c]	44 (10.1)	7 (4.2)	37 (13.7)	0.001[d]
Antibiotics[c]	30 (6.9)	7 (4.2)	23 (8.5)	0.087[d]
Pulmonary infiltrates < 72 h[c]	161 (36.8)	53 (31.9)	108 (39.9)	0.096[d]
Follow-up parameters				
ICU stay in d[e]	5 (3—11)	5 (2–9)	5 (3—13)	0.061[f]
Intubation[c]	174 (39.8)	60 (36.1)	114 (42.1)	0.220[d]
Mechanical ventilation in h[e]	51 (9–191)	22 (8–126)	66 (11–209)	0.003[f]
Death[c]	55 (12.6)	15 (9)	40 (14.8)	0.080[d]

Positive microbiology samples: 24.5%
P. aeruginosa: in 3.7%

Table 2
Pathogen diagnostics.

Variable	Population n = 437 (100)	PAI n = 166 (38)	PAA n = 271 (62)	p-value[a]
Positive sample < 72 h	107 (24.5)	32 (19.3)	75 (27.7)	0.048
P. aeruginosa	16 (15)	1 (3.1)	15 (20)	0.025
ATB; inadequate	24 (22.4)	11 (34.4)	13 (17.3)	0.053
P. aeruginosa (overall)	16 (3.7)	1 (0.6%)	15 (5.5%)	0.008
ATB escalated < 72 h	27 (6.2)	3 (1.8)	24 (8.9)	0.003
ATB inadequate (overall)	24 (5.6)	11 (6.6)	13 (4.8)	0.053

J Crit Care. 2021 Oct;65:49-55.

Routine use of antipseudomonal antibiotic

- 30-day ICU mortality (p=0.113): **20.4% (PAI)** vs. **29.3% (PAA)**

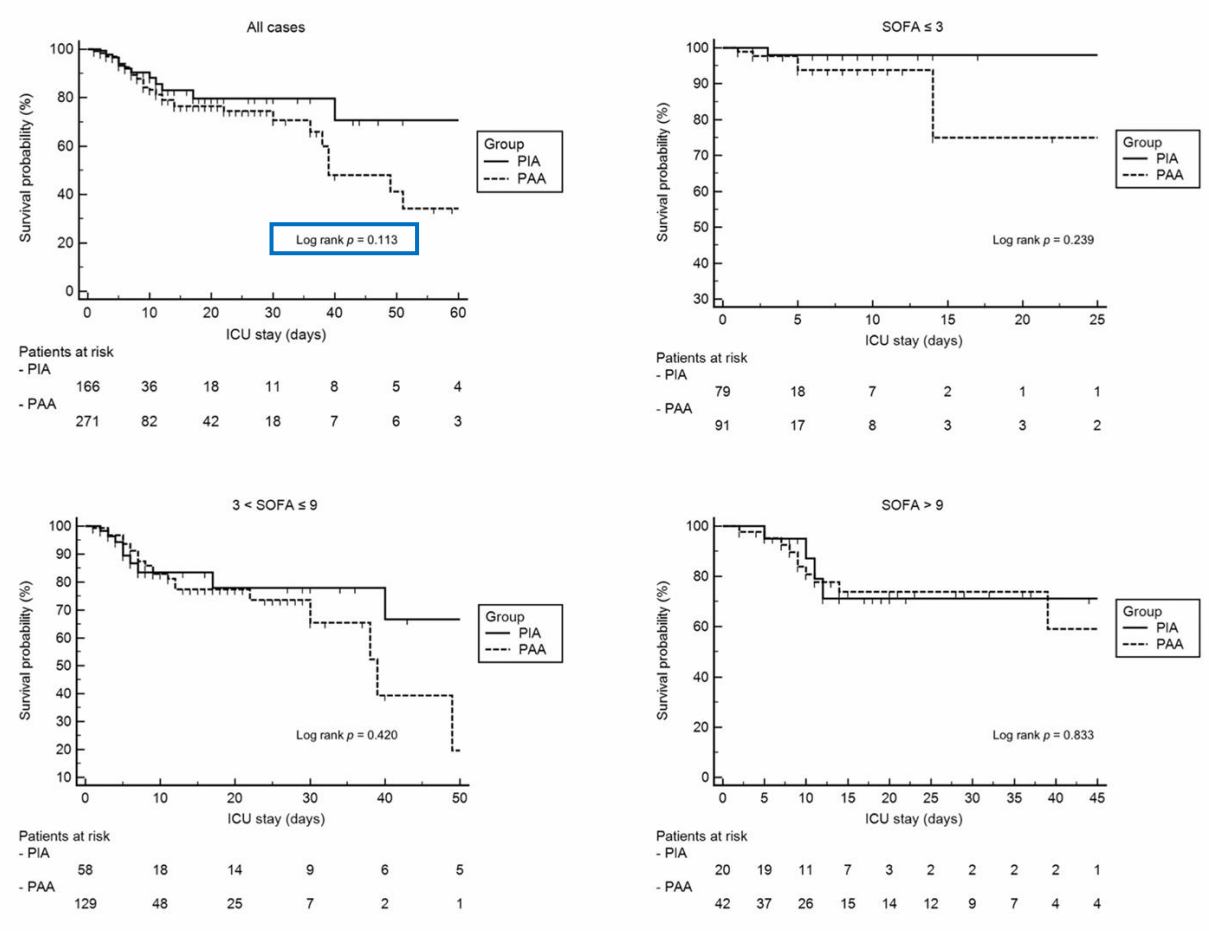


Table 3
Cox's proportional hazards model for survival time outcomes.

Variable		Cases (n)	Hazard ratio	95% CI	p-value
ATB	PAI[a]	157			
	PAA	262	1.73	0.92–3.26	0.089
$SOFA_i$	SOFA ≤3[a]	170			
	3 < SOFA ≤9	187	1.77	0.73–4.33	0.208
	SOFA > 9	62	1.77	0.67–4.69	0.251
Sex	Male[a]	223			
	Female	196	0.81	0.47–1.39	0.442
Age		419	1.03	1.00–1.06	0.043

- Empiric use of antipseudomonal antibiotics: **no associated with ICU survival**

J Crit Care. 2021 Oct;65:49-55.

Respiratory viral infections on mortality

- National prospective study in Canada (46 hospitals)
- Hospitalized AECOPD during winter seasons (2011–2015)
- Nasopharyngeal swabs for diagnosis of viral infection
- **Primary outcomes: 30-day mortality and ICU admissions**
- Viral infection
  - **admission to ICU (OR 1.5, 95% CI 1.2–1.9)↑**
  - **need for MV (OR 1.9, 95% CI 1.4–2.5)↑**
  - mortality (OR 1.1, 95% CI 0.8–1.4)→

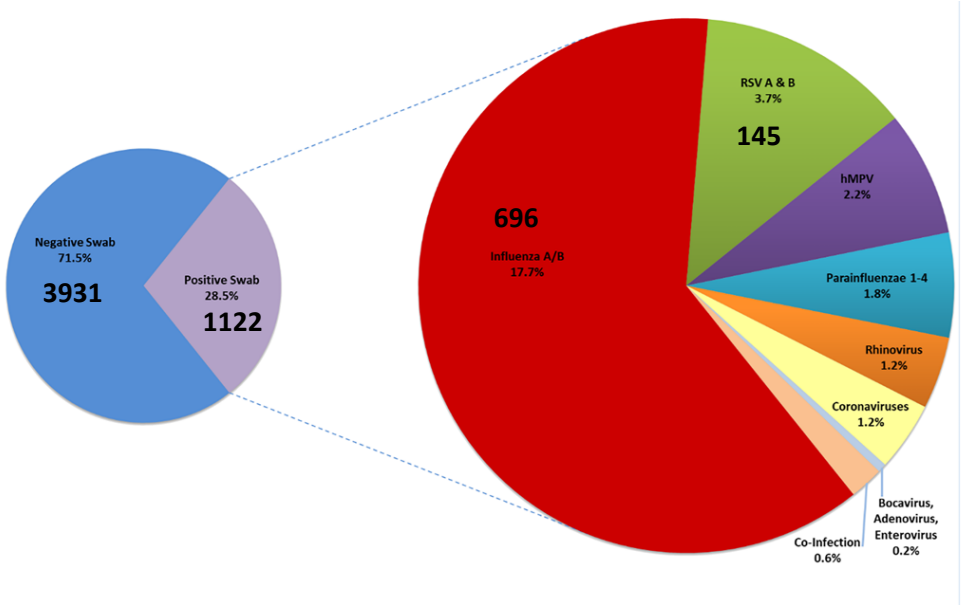


TABLE 1 Baseline characteristics among hospitalized patients with COPD who were tested for respiratory viruses with RV15 multiplex PCR during 2011–2015 winter seasons, n = 3931

Variable	Positive NP swab N = 1122	Negative NP swab N = 2809	p value
Age (mean ± SD) in years	73 ± 12.37	73 ± 11.34	0.86
Age strata (n, %)			
50–64 years	250 (22.3)	592 (21.1)	0.05
65–75 years	319 (28.4)	907 (32.3)	
>75 years	517 (46.1)	1247 (44.3)	
Female sex (n, %)	561 (50)	1372 (48.8)	0.53
BMI kg/m^2 ≤ 18.5 (n, %)	73 (7.01)	293 (11.1)	<0.001
Active smoking (n, %)	348 (32.8)	825 (29.6)	0.32
Heart disease (n, %)	587 (52.3)	1563 (55.6)	0.06
Kidney disease (n, %)	161 (14.4)	496 (17.7)	0.01
Immunocompromised state (n, %)	249 (22.2)	602 (21.4)	0.61
Malignancy[a] (n, %)	245 (21.8)	653 (23.3)	0.34
Rheumatic disease (n, %)	74 (6.6)	242 (8.6)	
HIV (n, %)	5 (0.45)	19 (0.68)	
Use of home oxygen (n, %)	150 (13.4)	535 (19.1)	<0.001
Assisted living dwelling prior to admission (n, %)	140 (12.5)	282 (10.1)	0.03
Long-term care dwelling prior to admission (n, %)	95 (8.5)	170 (6.1)	0.007
Baseline frailty index[b] (median IQR)	0.22 (0.15–0.3)	0.23 ± (0.16–0.3)	0.37
Unknown (n, %)	362 (32.3)	728 (25.9)	
Influenza vaccination status			
Vaccinated (n, %)	700 (65.8)	1887 (68.9)	0.06
Not vaccinated (n, %)	364 (34.2)	848 (31)	
Unknown (n, %)	58 (5.17)	74 (2.6)	
Clinical diagnosis of pneumonia (n, %)	435 (38.8)	1430 (50.9)	<0.001
Admitting diagnosis of COPD exacerbation (n, %)	584 (52.05)	1306 (46.49)	0.002
30-day mortality (n, %)	84 (7.5)	222 (7.9)	0.69
Admission to intensive care (n, %)	185 (16.5)	350 (12.5)	0.001
Mechanically ventilated (n, %)	105 (9.4)	158 (5.7)	<0.001
Use of non-invasive ventilation (n, %)	135 (14.1)	322 (12.9)	0.34

Influenza Other Respir Viruses. 2022 Nov;16(6):1172-1182.

Air pollution and viral infection in severe AECOPD

- AECOPD at 28 hospitals in South Korea
- Viral pathogens: 36.7% (270 of 735)

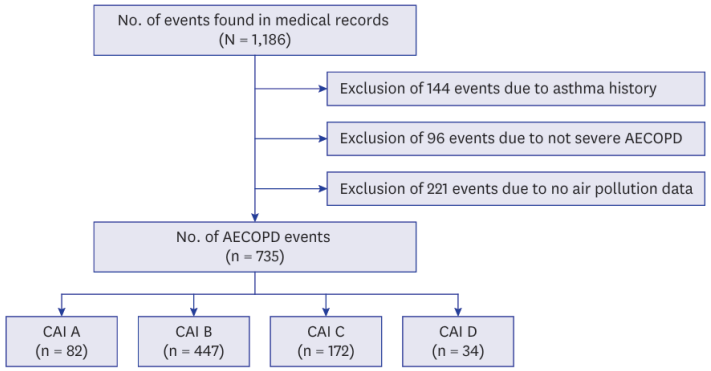
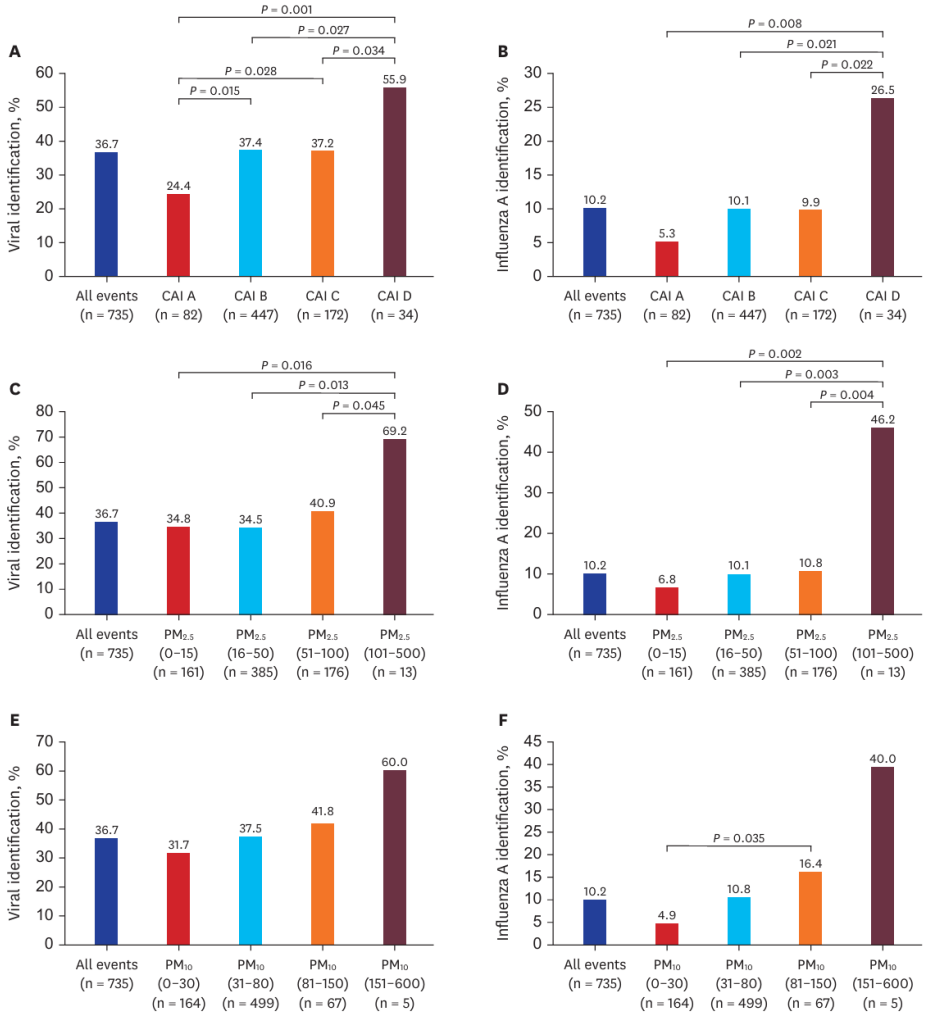


Fig. 1. Study design.
AECOPD = acute exacerbation of chronic obstructive pulmonary disease, CAI = comprehensive air-quality index.

Supplementary Table 1. Relationship between CAI value and each air pollutant

Category	A	B	C	D
Description	Good	Moderate	Unhealthy	Very unhealthy
Value	0–50	51–100	101–250	251–500
PM_{10}, μg/m³	0–30	31–80	81–150	151–600
$PM_{2.5}$, μg/m³	0–15	16–50	51–100	101–500
O_3, ppm	0–0.030	0.031–0.090	0.091–0.150	0.150–0.600
NO_2, ppm	0–0.030	0.031–0.060	0.061–0.200	0.201–2
SO_2, ppm	0–0.020	0.021–0.050	0.051–0.150	0.151–1
CO, ppm	0–2	2.01–9	9.01–15	15.01–50

- Air pollution may exacerbate COPD by making patients vulnerable to viral infections



J Korean Med Sci. 2023 Mar 6;38(9):e68.

Antibiotics without obvious infection signs in AECOPD

- RCT in China
- **Hospitalized** AECOPD (n=816), 10/2018 ~ 12/2019
- Antibiotic group (n=406) : moxifloxacin 400 mg/day IV for 7 days
- Nonantibiotic group (n=410): placebo for 7 days

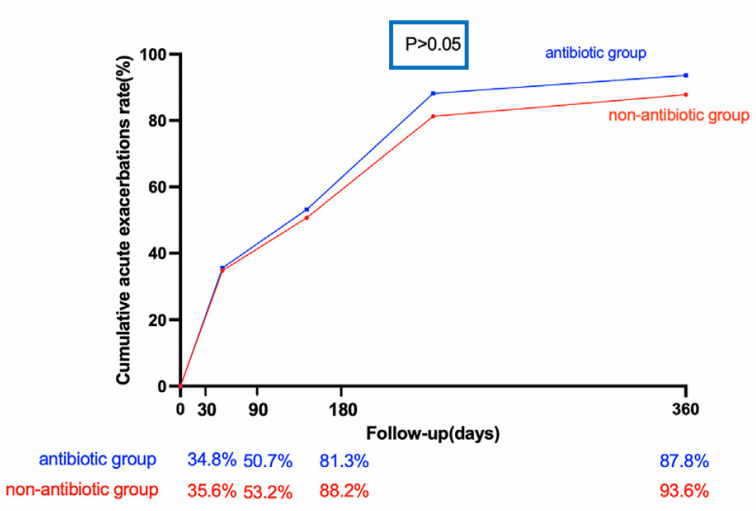


FIGURE 2
Cumulative acute exacerbation rates in the antibiotic group and nonantibiotic group.

TABLE 2 Secondary end points.

Items	Visit time (Day)	antibiotic group (n = 406)	Non-antibiotic group(n =410)	Statistics	P
Mortality	30	0	0	-	-
	90	2 (0.5)	2 (0.5)	0.009	0.992
	180	4 (1.0)	5 (1.2)	0.103	0.749
	360	7 (1.7)	7 (1.7)	0.003	0.985
CAT score	30	15.83 ± 0.34	15.73 ± 0.36	0.184	0.854
	90	14.57 ± 0.35	15.45 ± 0.31	1.860	0.063
	180	13.86 ± 0.33	14.54 ± 0.34	1.455	0.146
	360	13.85 ± 0.33	14.66 ± 0.30	1.805	0.072
rehospitalization rate	30	75 (18.8)	97 (23.6)	6.505	0.011
	90	116 (28.6)	125 (30.5)	0.360	0.548
	180	201 (49.5)	208 (50.70)	0.122	0.726
	360	275 (67.7)	279 (68.0)	0.009	0.923
ICU treatment rate	30	2 (0.5)	1 (0.2)	0.345	0.623
	90	8 (2.0)	7 (1.7)	0.078	0.780
	180	15 (3.7)	17 (4.1)	0.111	0.740
	360	21 (5.2)	19 (4.6)	0.127	0.722
The time from discharge to first acute exacerbation,day	-	45.64±1.12	43.97±1.57	0.874	0.382
The time of stay in hospital for the first time after discharge, day	-	5.84±0.16	6.75±0.57	1.504	0.026

Front Pharmacol. 2024 May 10;15:1380939.

Antibiotics without obvious infection signs in AECOPD

- Who may benefit from antibiotics
  - >62.5 years of age
  - **CRP >12.56 mg/L**
  - **Sputum viscosity** >III without obvious signs of infection

TABLE 3 Efficacy analysis of each indicators in the evaluation of prognosis.

Items	AUC (95% CI)	*P*	Cut-off	Sensitivity (%)	Specificity (%)	Yoden index
CRP	0.733 (0.582–0.884)	0.011	12.56	42.4%	94.5%	0.369
Sputum viscosity	0.756 (0.671–0.840)	0.001	3	95.7%	59.1%	0.548
Age	0.679 (0.626–0.732)	0.001	62.5	63.9%	52.3%	0.162

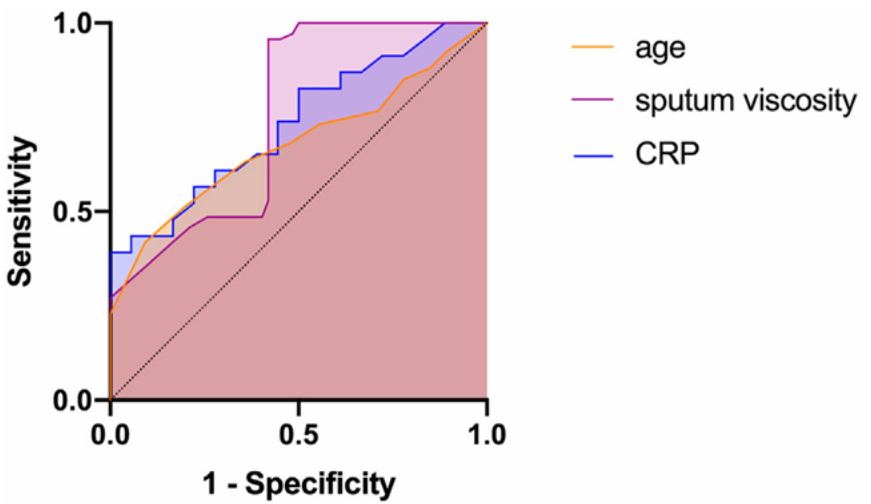


FIGURE 5
ROC analyses for age, CRP, and sputum viscosity in determining the prognosis.

Front Pharmacol. 2024 May 10;15:1380939.

Biomarkers for bacteria or virus

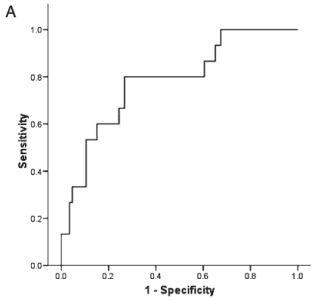
- Bacterial Exacerbations
- SPIROMICS (n = 1,544) and COPDGene (n = 602) cohorts
- 3,471 total exacerbations (1,044 severe)

Table 3. Negative Binomial Regression Severe Exacerbations (Prospective)

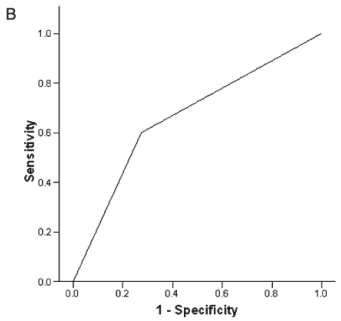
	SPIROMICS			COPDGene		
Biomarker	**β Coefficient**	***P* Value**	**FDR**	**β Coefficient**	***P* Value**	**FDR**
A2M	0.247	0.027	0.893	0.461	0.003	0.072
CCL16	−0.047	0.599	0.914	0.317	0.043	0.348
CEACAM1	0.113	0.152	0.914	0.385	0.026	0.256
CXCL10	0.194	0.044	0.893	0.080	0.661	0.865
CXCL9	0.252	0.017	0.893	0.165	0.318	0.673
DCN	0.047	0.622	0.929	0.585	0.000	0.001
IgM	−0.079	0.384	0.914	0.307	0.022	0.250
IL16	0.000	0.998	0.998	−0.383	0.008	0.114
IL18BP	0.168	0.050	0.893	0.023	0.865	0.961
MDA_LDL_log*	0.057	0.865	0.985	0.838	0.039	0.348
MICA_log*	−0.259	0.250	0.914	0.838	0.003	0.072
SERPINA1	−0.030	0.743	0.929	0.521	0.001	0.061
SERPINE1	−0.196	0.038	0.893	0.062	0.724	0.903
SLPI	−0.055	0.561	0.914	−0.317	0.019	0.246
SPINK1	0.118	0.160	0.914	−0.333	0.006	0.101

- No biomarker for bacterial exacerbation

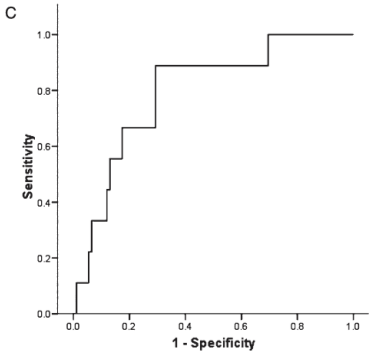
- **Serum IP-10** as a biomarker of **HRV** Infection at AECOPD



(A) IP-10, AUC = 0.78 (0.65-0.91)



(B) Coryzal symptoms, AUC = 0.66 (0.51-0.82)



(C) IP-10 + coryzal symptoms, AUC = 0.80 (0.66-0.94)

- AUC of serum IP-10 alone for detecting a HRV infection at exacerbation

Am J Respir Crit Care Med. 2017 Feb 15;195(4):473-481.
Chest. 2010 Apr;137(4):812-22.

Antibiotics

- Antibiotics, when indicated, can **shorten recovery time**, **reduce the risk of early relapse**, **treatment failure**, and **hospitalization duration**.

Table I Anthonisen classification of COPD exacerbations based on cardinal symptoms. Based on data from Anthonisen and colleagues (1987)

Severity of exacerbation	Type of exacerbation	Characteristics
Severe	Type 1	Increased dyspnea, sputum volume and sputum purulence
Moderate	Type 2	Any 2 of the above 3 cardinal symptoms
Mild	Type 3	Any 1 of the above 3 cardinal symptoms and 1 or more of the following minor symptoms or signs - Cough - Wheezing - Fever without an obvious source - Upper respiratory tract infection in the past 5 days - Respiratory rate increase >20% over baseline - Heart rate increase >20% over baseline

COPD 급성악화 환자에서 3가지 주요증상: **호흡곤란** 악화, **가래양**의 증가, **화농성** 객담의 증가
Type I (호흡곤란↑ + 가래 양↑ + 가래 농도↑): 항생제 권장
Type II (두 가지 이상): 특히 화농성 객담이 포함되면 **항생제 투여 권장**
Type III (한 가지 증상): 항생제 권장하지 않음

COPD. 2020 Jun;17(3):311-317.

Antibiotics

- Meta-analysis (6 observational studies)
- Sputum purulence: green or yellow sputum by visual assessment of color
- **Purulent sputum**: higher probability of **positive bacterial culture results** than mucoid sputum (**RR = 2.14**, 95%CI [1.25, 3.67], p=0.006)

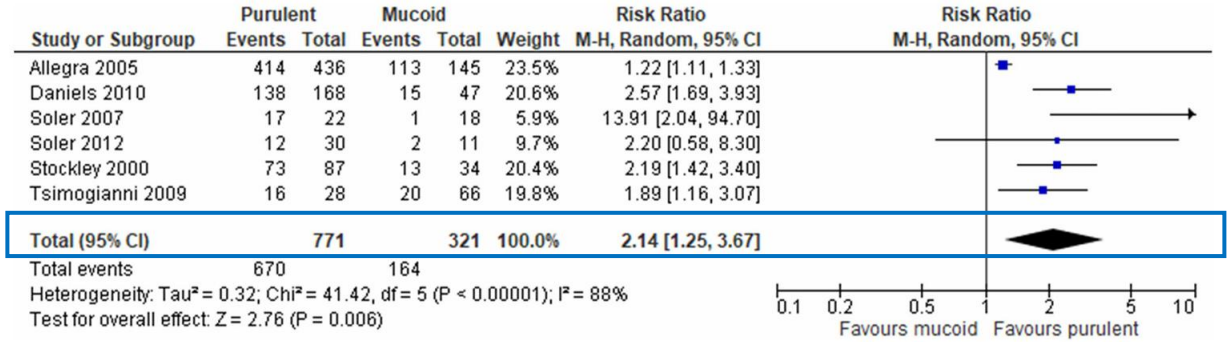


Figure 2. Forest plot of purulent versus mucoid sputum samples on sputum culture results.

COPD. 2020 Jun;17(3):311-317.

Predictors of failure without antibiotics

- Mild to moderate AECOPD (n=310), 2007 ~ 2010
- Multicenter, double blind RCT: AMX/clavulanate 500/125 mg tid for 8 days vs. placebo (n=152)
- Analysis of **placebo group** to assess the **predictors of failure without antibiotics**

Table 1—*Baseline Characteristics of the Population Treated Without Antibiotics According to the Exacerbation Type*

Characteristic	Type 1[a] (n = 45)	Type 2[b] (n = 72)	Type 3[c] (n = 35)	*P* Value
Age, y	71.3 ± 8.7	65.9 ± 11.8	68.1 ± 10.7	.058
Male sex	41 (91.1)	52 (72.2)	26 (74.3)	.044
Smoking status				
Current	30 (66.7)	43 (59.7)	16 (45.7)	.162
Former	15 (33.3)	29 (40.3)	19 (54.3)	
Pack-y	41.8 ± 13.7	36.1 ± 21.0	36.4 ± 21.0	.260
High BP	24 (53.3)	33 (45.8)	16 (45.7)	.697
Diabetes mellitus	10 (22.2)	12 (16.7)	6 (17.1)	.734
Coronary heart disease	8 (17.8)	7 (9.7)	4 (11.4)	.429
FVC, mL	2,552.0 ± 865.0	2,961.5 ± 1017.2	2,627.7 ± 874.4	.049
FVC, % predicted	69.4 ± 17.9	73.9 ± 18.6	68.9 ± 18.2	.280
FEV_1, mL	1,523.1 ± 574.9	1,879.0 ± 673.5	1,656.0 ± 586.3	.010
FEV_1, % predicted	62.6 ± 11.2	68.1 ± 13.4	65.5 ± 9.5	.056
FEV_1/FVC ratio	59.5 ± 5.8	63.5 ± 5.8	63.0 ± 4.7	.001
Treatment of the exacerbation				
Short-acting β-agonists	20 (44.4)	19 (26.4)	14 (40.0)	.105
Oral corticosteroids	15 (33.3)	9 (12.5)	3 (8.6)	.004
CRP level	42.0 (23.8-60.3)	21.9 (9.1-34.6)	20.7 (11.3-30.1)	< .001

Data are presented as mean ± SD, No. (%), or median (interquartile range). CRP = C-reactive protein.
[a]Type 1: all Anthonisen criteria present (increased dyspnea, increased sputum volume, and increased sputum purulence).
[b]Type 2: only two Anthonisen criteria present.
[c]Type 3: only one Anthonisen criterion present.

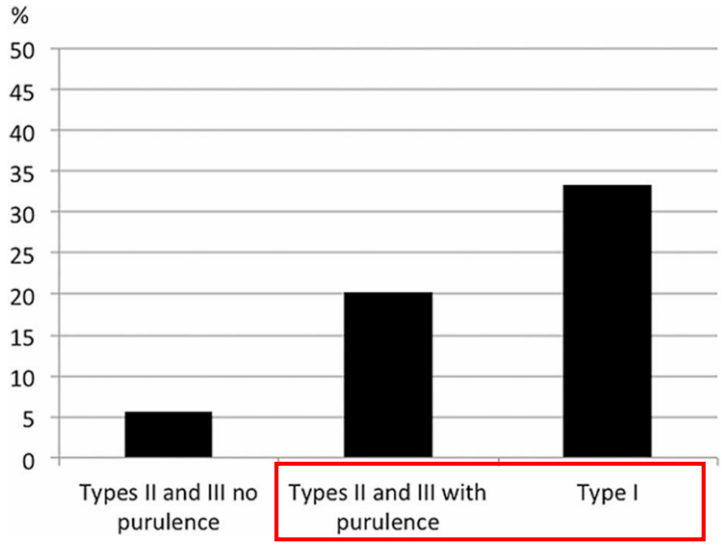


FIGURE 1. Percentage of failure rates in exacerbations of mild to moderate COPD not treated with antibiotics according to Anthonisen criteria.

- Among the Anthonisen criteria, only an increase in **sputum purulence** is a significant **predictor of failure without antibiotics**.

Chest. 2013 Nov;144(5):1571-1577.

Predictors of failure without antibiotics

- Predictive value for clinical failure (P=0.033)
  - **Anthonisen criteria: AUROC 0.708 (0.616-0.801)**
  - **CRP> 40 mg/L: AUROC 0.842 (0.760-0.924)**

Table 2—*Univariate and Multivariate Logistic Regression Analysis of Exacerbation Factors That Predict Clinical Failure of Exacerbations of Mild to Moderate COPD Not Treated With Antibiotics*

	Univariate		Multivariate		Multivariate With CRP	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Increased dyspnea	1.6 (0.6-3.8)	.32	2.3 (0.9-5.9)	.078	1.3 (0.4-3.9)	.32
Increased sputum volume	2.1 (0.7-6.5)	.20	1.8 (0.6-6.1)	.32	0.6 (0.2-2.4)	.20
Increased sputum purulence	5.9 (1.7-20.7)	.005	6.3 (1.8-22.5)	.005	6.1 (1.5-25.0)	.005
CRP level ≥ 40 mg/L	13.4 (5.3-34.3)	< .001	NA	…	13.4 (4.6-38.8)	< .001

NA = not assessed. See Table 1 legend for expansion of other abbreviation.

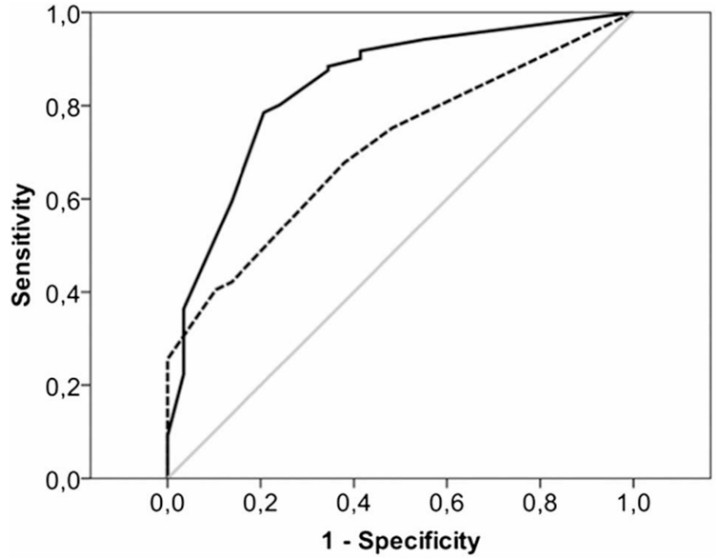


FIGURE 2. Receiver operating characteristic curves showing the predictive value for clinical failure of Anthonisen criteria (dotted line) (area under the curve, 0.708; 95% CI, 0.616-0.801) and with the addition of a C-reactive protein level ≥ 40 mg/L (solid line) (area under the curve, 0.842; 95% CI, 0.760-0.924) among patients with exacerbations of mild to moderate COPD not treated with antibiotics. Differences between curves were significant at $P = .033$.

- The use of a point-of-care **CRP** test significantly increases the predictive accuracy of failure.

Chest. 2013 Nov;144(5):1571-1577.

CRP-guided antibiotics in hospitalized AECOPD

- Multicenter RCT, hospitalised AECOPD, 2011 ~ 2015
- Antibiotic treatment: AMX/CLV (625mg, tid for 7 days)
  - **GOLD strategy (n=119): sputum purulence** in combination with increased dyspnoea and/or increased sputum volume
  - **CRP strategy (n=101): CRP ⩾50 mg/L**
- **Fewer antibiotics in the CRP group** compared to the GOLD group (31.7% versus 46.2%, p=0.028)
- **Similar 30-day treatment failure rate**, **time to next exacerbation**, and **length of stay**

TABLE 2 Primary and secondary endpoints for the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and C-reactive protein (CRP) groups

	GOLD-group (n=119)	CRP-group (n=101)	Difference	Bootstrap 95% CI	p-value
Primary endpoint					
Patients treated with antibiotics	55 (46.2)	32 (31.7)	−14.5	−1.9 to −26.9	0.028
Secondary endpoints					
30-day treatment failure rate	53 (44.5)	46 (45.5)	1.0	−14.7 to 11.7	0.881
Time to next exacerbation days	28 (3–209)	32 (0–327)	4	−57.9 to 19.1	0.713
LOS days	6 (4–8)	7 (4–9)	1.0	−0.1 to 2.7	0.167
Change in CCQ score on day-30	−1.00 (−1.95 to −0.20)	−0.90 (−1.40 to −0.1)	−0.1	−0.54 to 0.16	0.336
Change in LRTI-VAS score on day-30	−8.5 (−14.0 to −3.0)	−7.5 (−15.0 to −2.0)	1.0	−2.3 to 2.9	0.723

Eur Respir J. 2019 May 23;53(5):1802014.

Summary

- Exacerbation of COPD: increased local and systemic inflammation caused by airway infection (mostly virus or bacteria)
- Bacterial exacerbation
  - Acquisition of new bacterial strain, impaired innate alveolar macrophage response, host response to bacteria
  - As the number of comorbidities increased, the risk of bacterial infection increased
  - P. aeruginosa and MDRO: poorer outcomes
  - Empiric use of antipseudomonal antibiotics: low evidence
- Viral exacerbation
  - Frequent exacerbators: more HRV infection
  - Secondary bacterial infection is common after viral infection
  - Bacterial coinfection
    - greater fall of FEV1
    - higher symptom count
    - higher bacterial loads
- Antibiotics use in AECOPD
  - Purulent sputum: higher probability of positive bacterial culture
  - Purulent sputum and CRP: predictors of failure without antibiotics