Acute Exacerbation of Idiopathic Pulmonary Fibrosis

A Brief Update

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Disclosures

- I have contracts with the following commercial entities:
  - aTyr Pharmaceuticals, Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Global Blood Therapeutics, Genoa, ImmuneWorks, Moerae Matrix, Navitor, Parexel, Patara, PharmAkea, Prometic, Takeda, Toray, Xfibra
- I have grants/contract with the following non-commercial entities:
  - NIH/NHLBI, NIH/NCATS, Pulmonary Fibrosis Foundation

ACUTE EXACERBATION

What are we talking about?

Case presentation

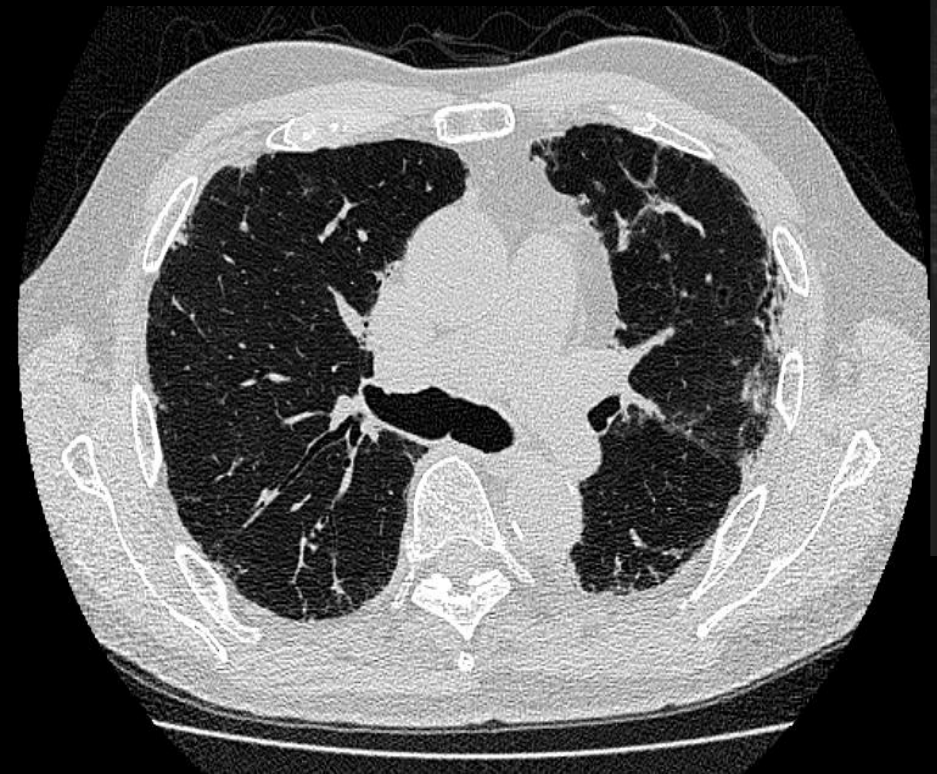
- 67 year old man
- Reports dyspnea on exertion (2 flights of stairs)
  - PMH: Hypertension, GERD
  - Meds: HCTZ, omeprazole
  - Social: former smoker, retired dentist
  - Family: no history of ILD

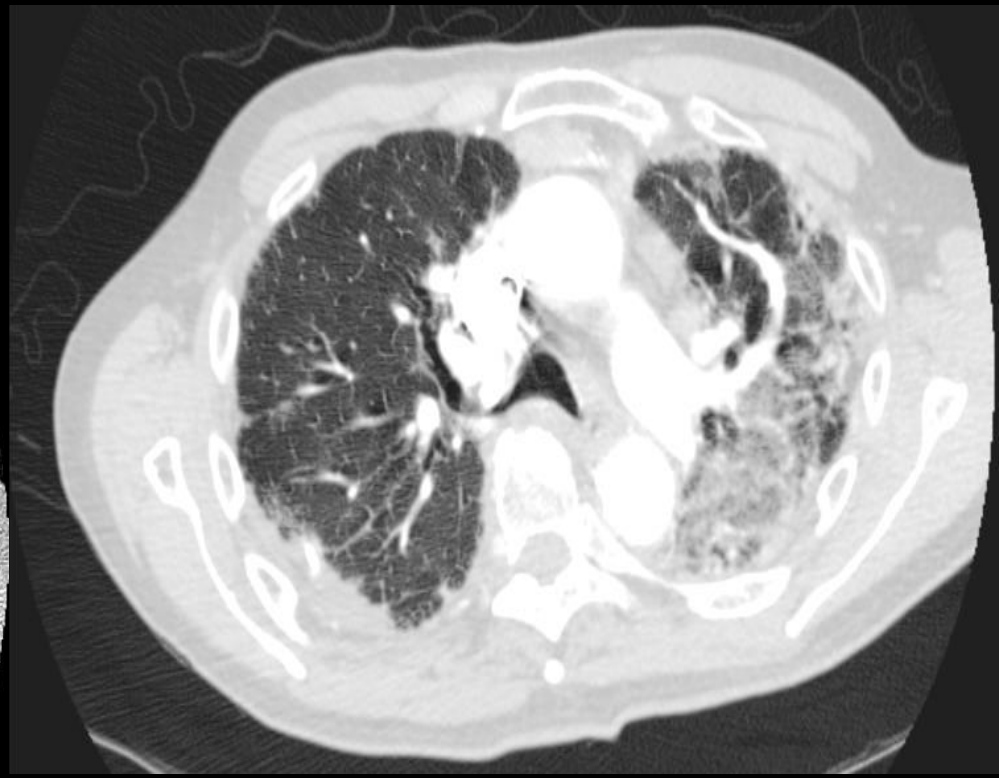
- 96% RA (88% walking)
- Dry inspiratory crackles at both bases

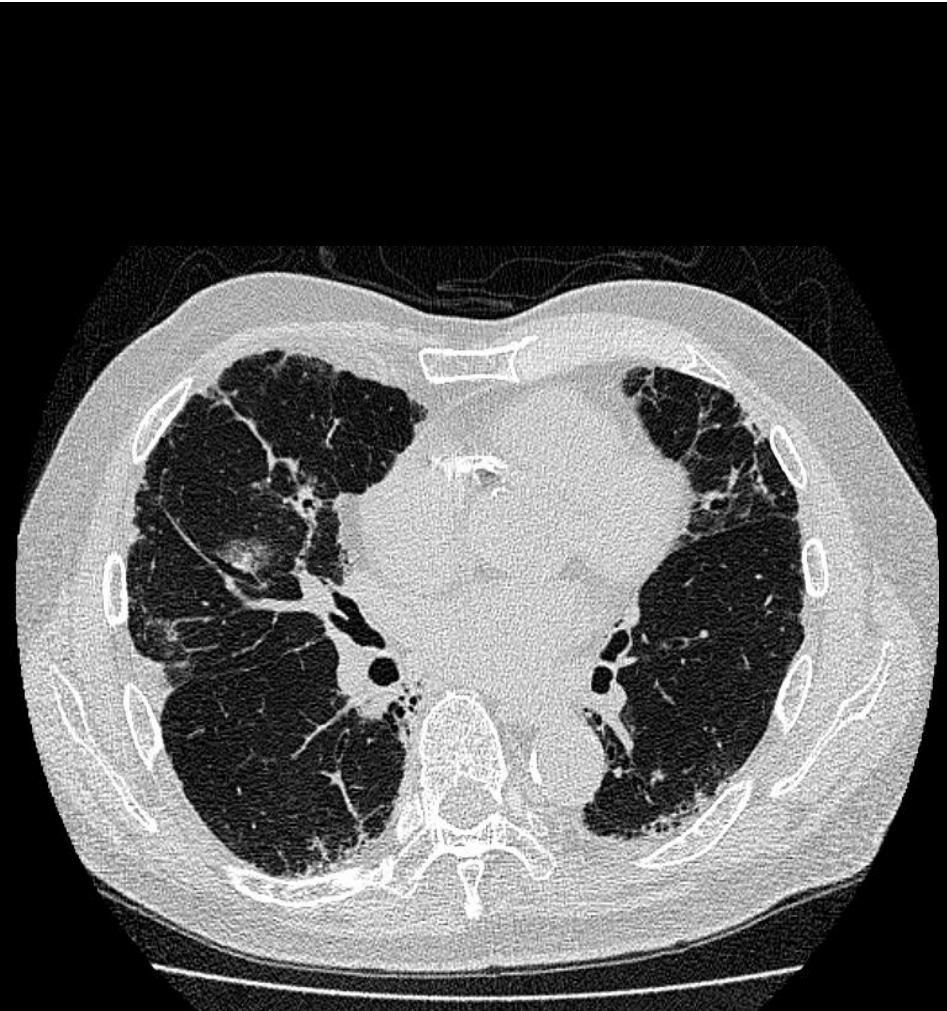
Case Presentation

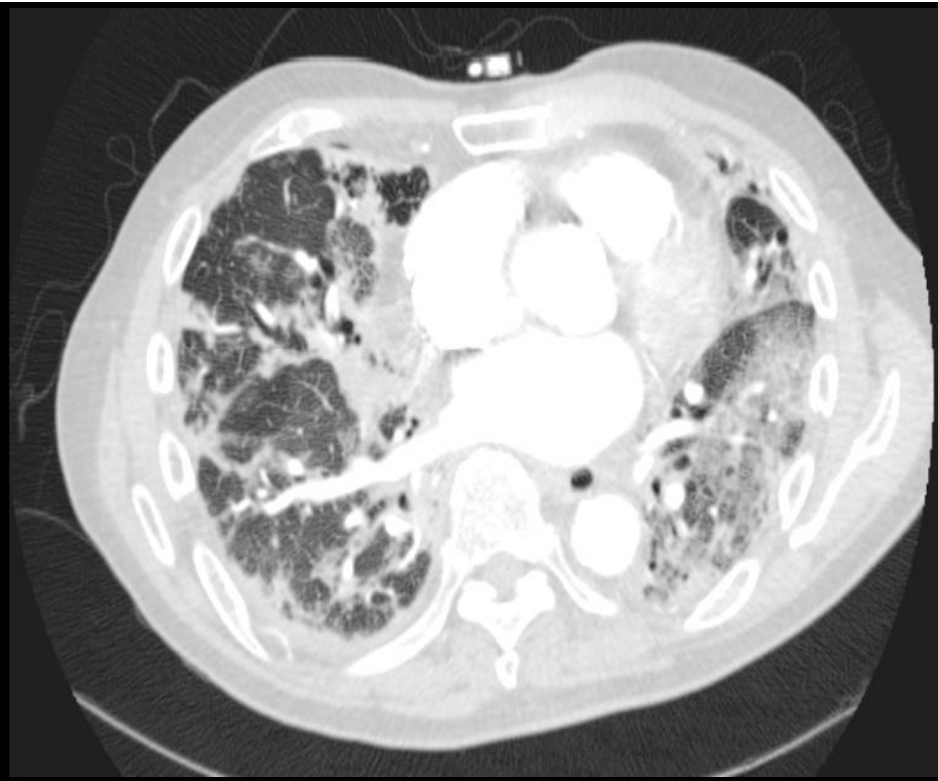
- Patient diagnosed with IPF
- Started on “antifibrotic” therapy

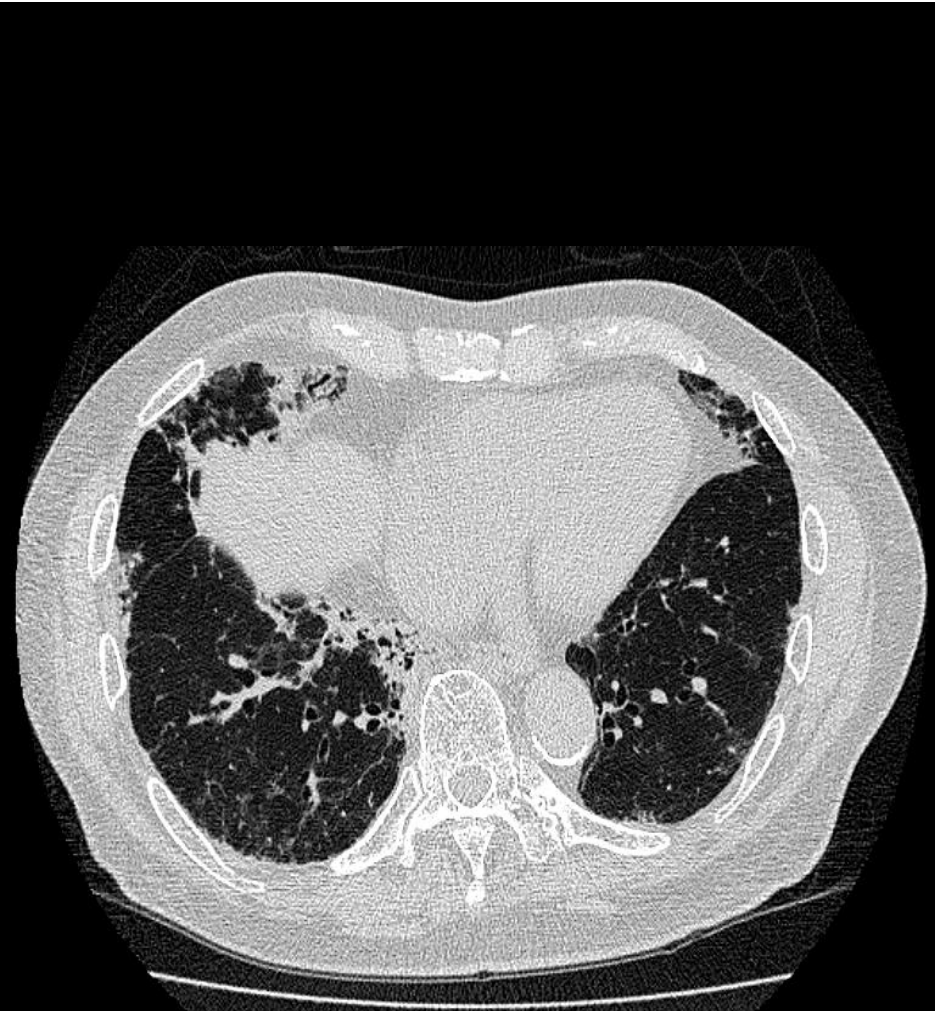
- 4 months later, worsened dyspnea and cough over days
- Recent flu-like symptoms
- On exam, afebrile, slightly tachypneic, 85% on room air

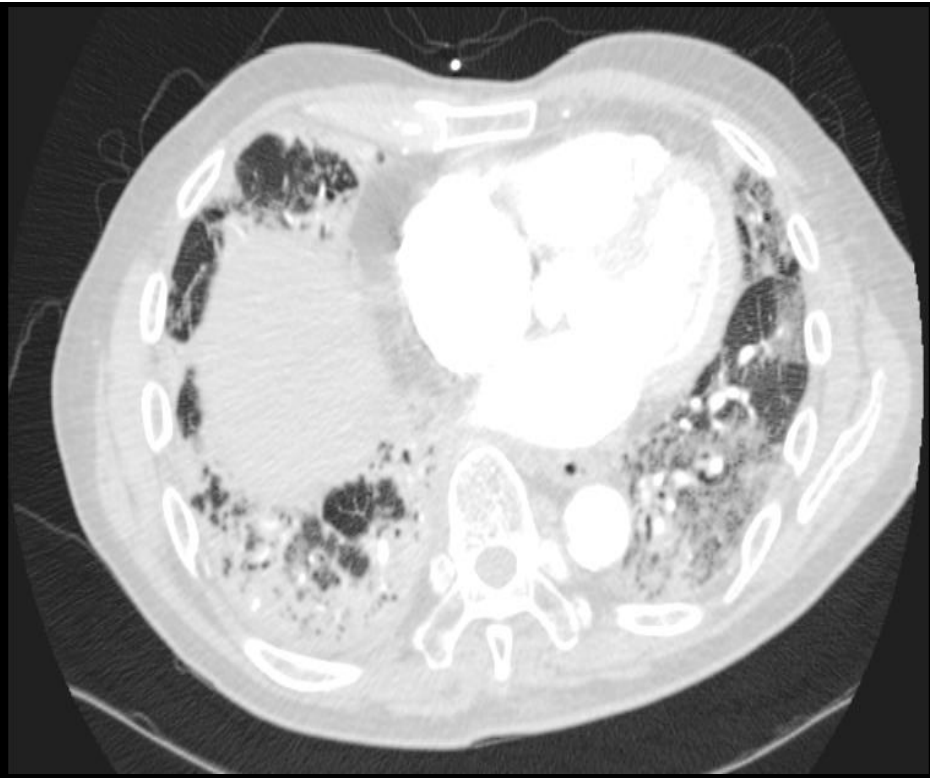




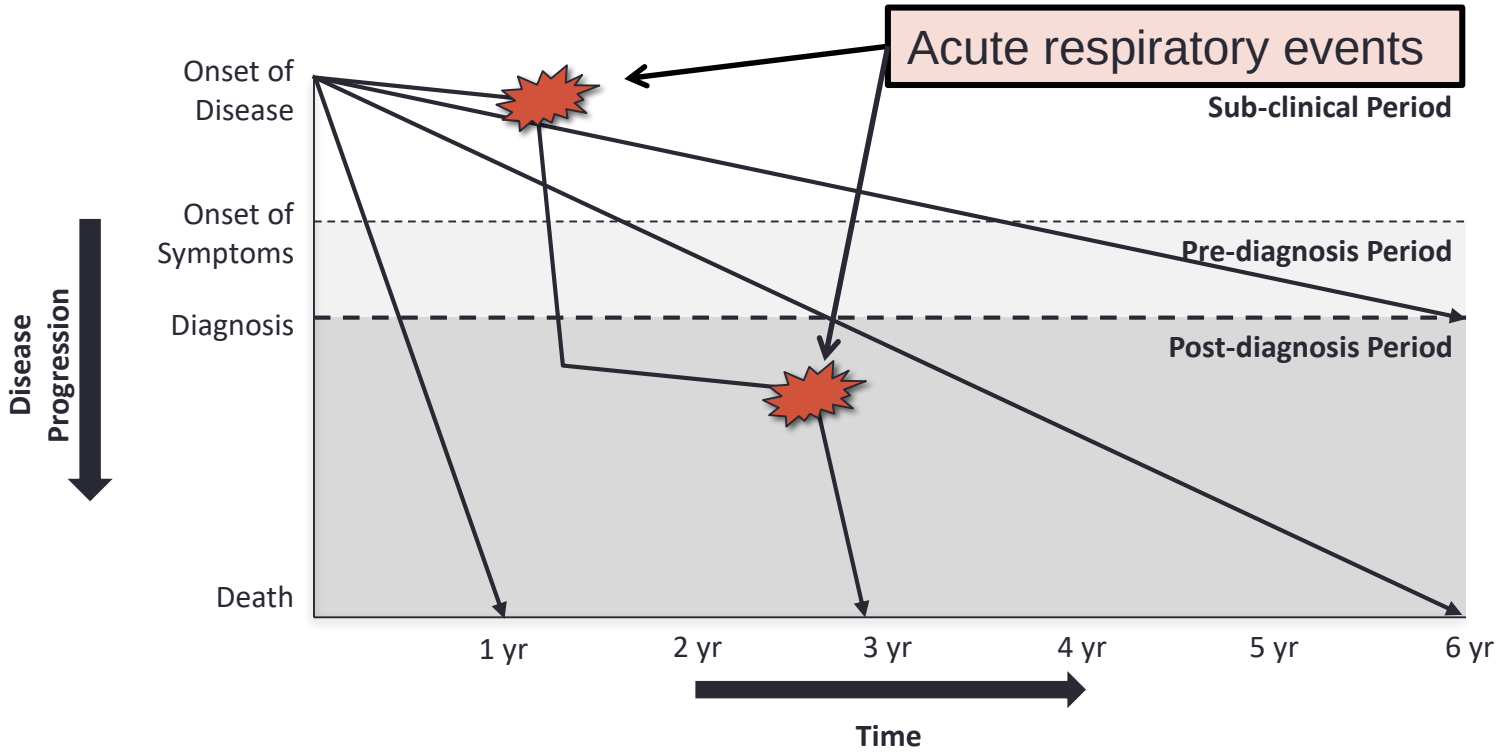








IPF natural history



Ley et al. AJRCCM 2011;183:431

Acute respiratory events

- Infection
  - Pneumonia
  - Bronchitis
- Cardiogenic edema
- Pulmonary embolism
- Pneumonitis
  - Drug toxicity
  - Aspiration
- Pleural effusion
- Pneumothorax

- **Idiopathic**

In IPF, we have considered “idiopathic” acute respiratory events a distinct clinical entity termed **acute exacerbation**

Acute exacerbation of IPF

- ***"an acute, clinically significant deterioration of unidentifiable cause in a patient with underlying IPF."***

Diagnostic Criteria
Previous or concurrent diagnosis of IPF
Unexplained worsening of dyspnea within 30 days
HRCT with new ground glass and/or consolidation
No evidence of pulmonary infection by BAL or ET aspirate
Exclusion of other alternative causes (e.g. CHF, PE)

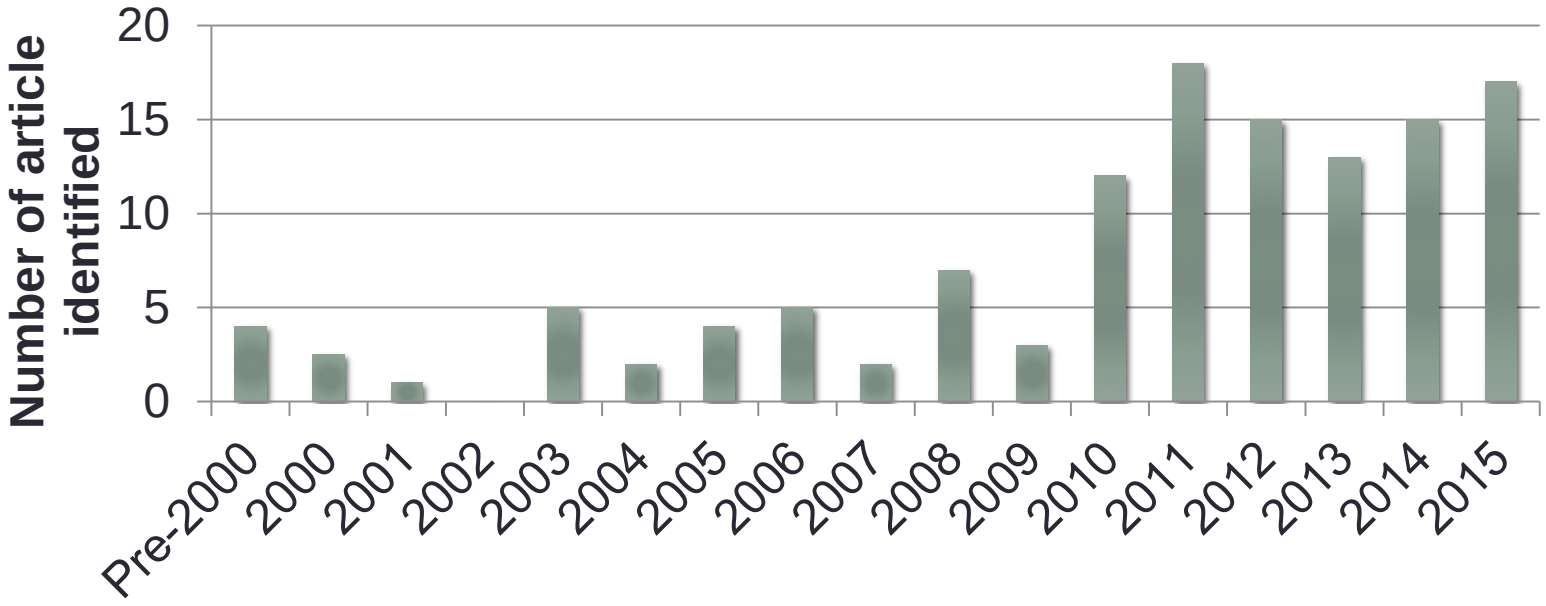
Collard et al. AJRCCM 2007;176:636

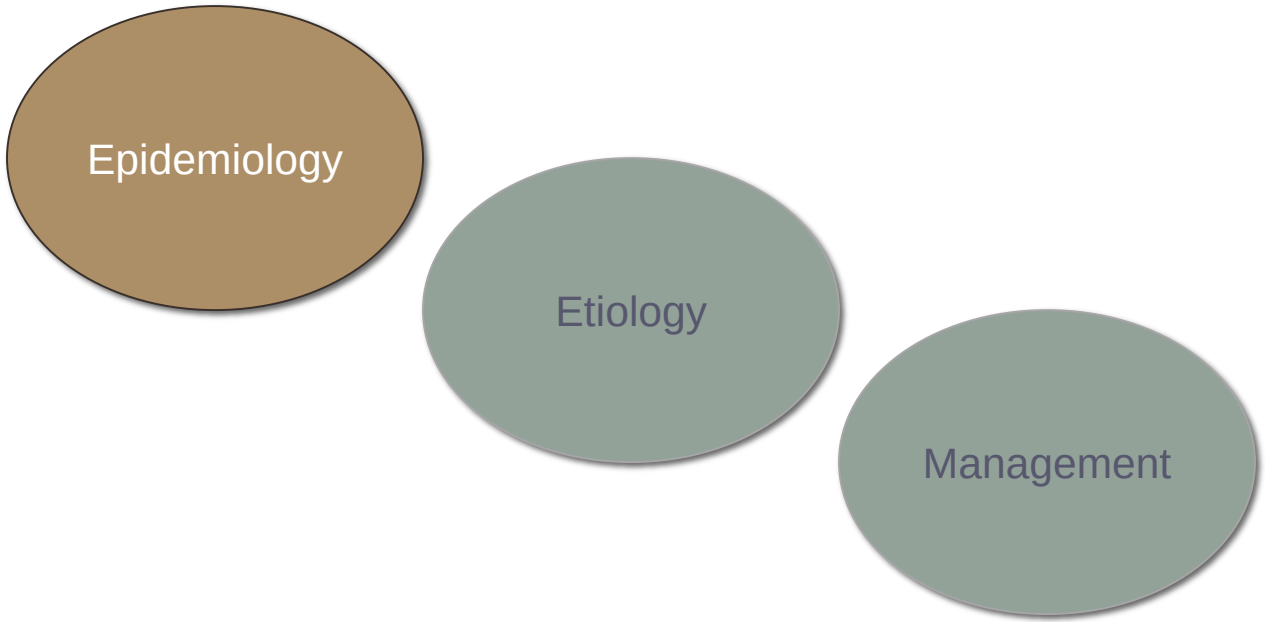
ACUTE EXACERBATION

What have we learned?

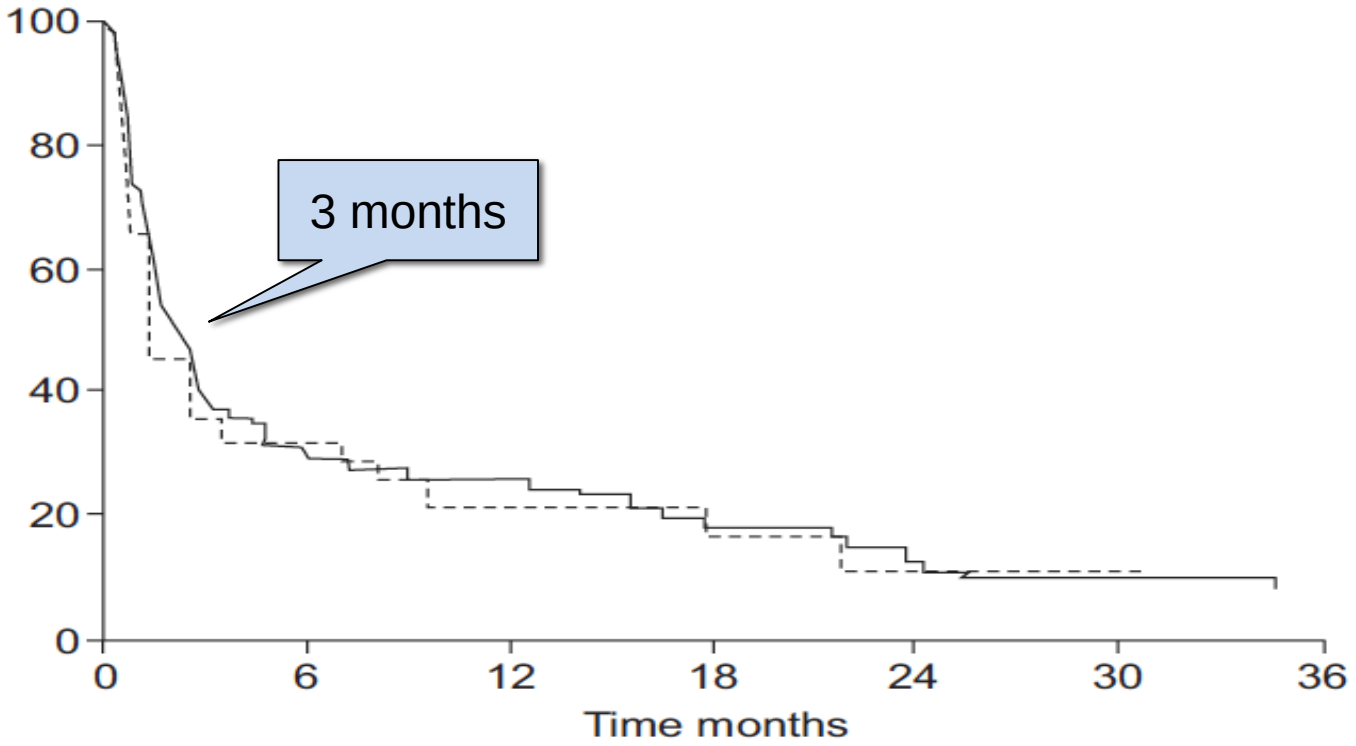
Original research articles by year

- Research on acute exacerbation has grown!




Epidemiology
Etiology
Management

Short-term mortality



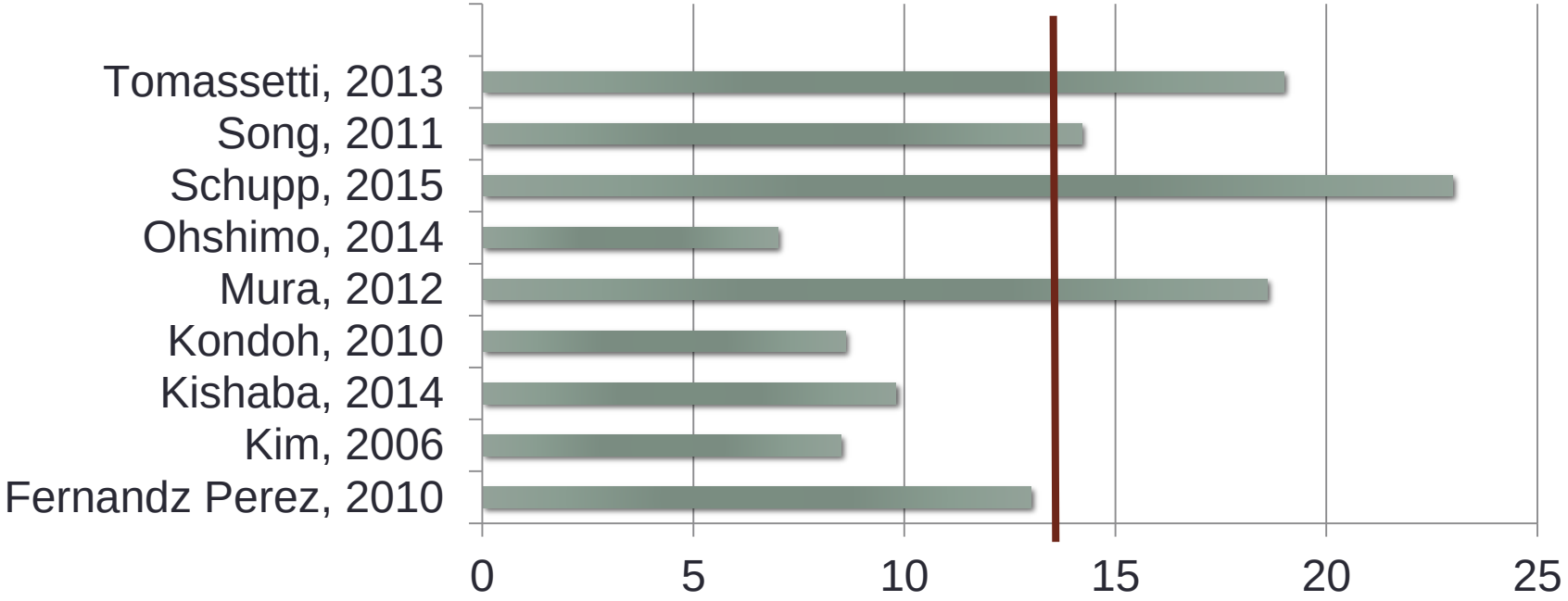
Song ERJ 2011;37:356

Incidence

- There is disagreement among experts regarding the incidence of acute exacerbation
  - In general, clinicians believe they are “common”
  - In general, clinical researchers believe they are “uncommon”

Incidence from clinical cohorts

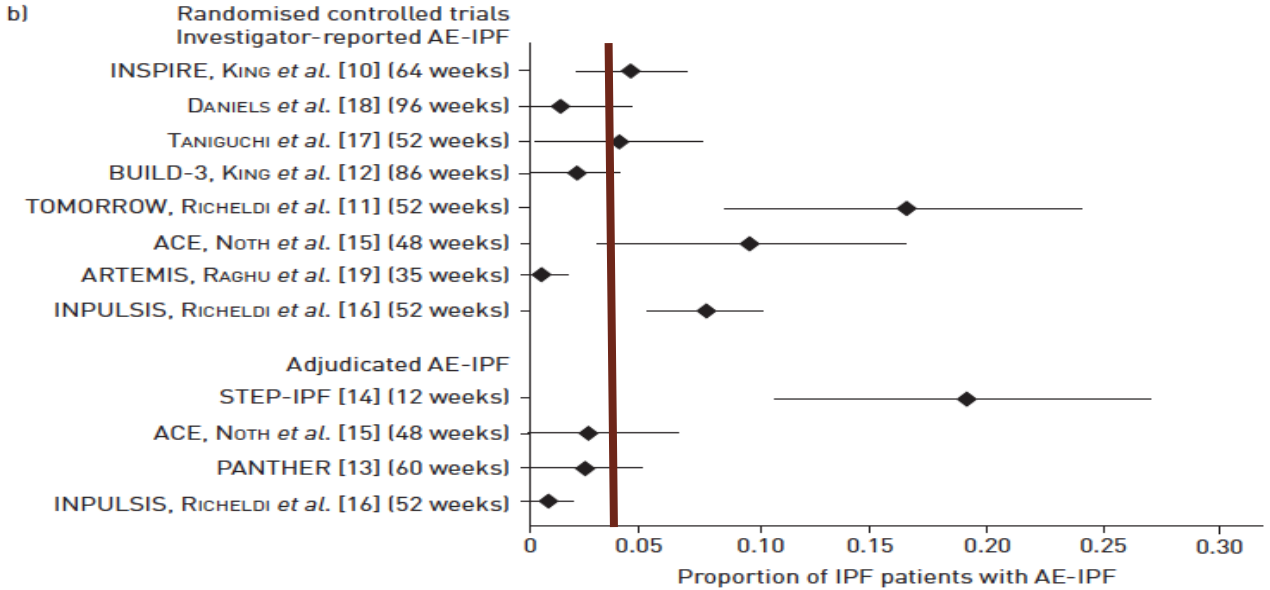
- Non-weighted average incidence of **13.5%/year**



Collard AJRCCM 2016;194:265

Incidence from clinical trials

- Meta-analysis of 6 clinical trials reported weighted average incidence of **4.1%/year**

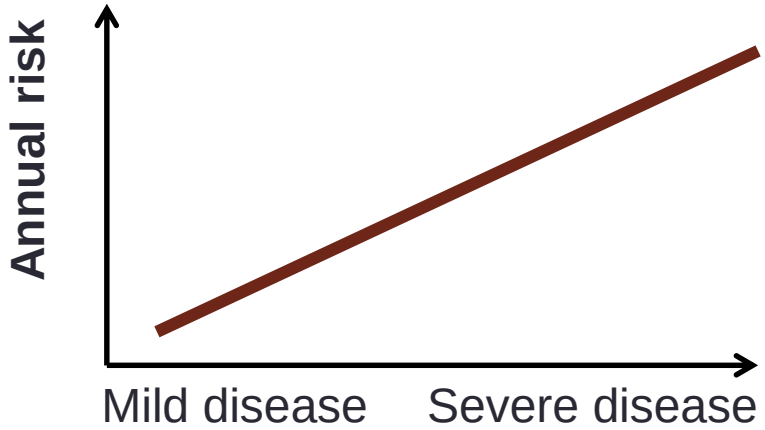


Atkins Resp Med 2014;108:376; Ryerson ERJ 2015;46:512

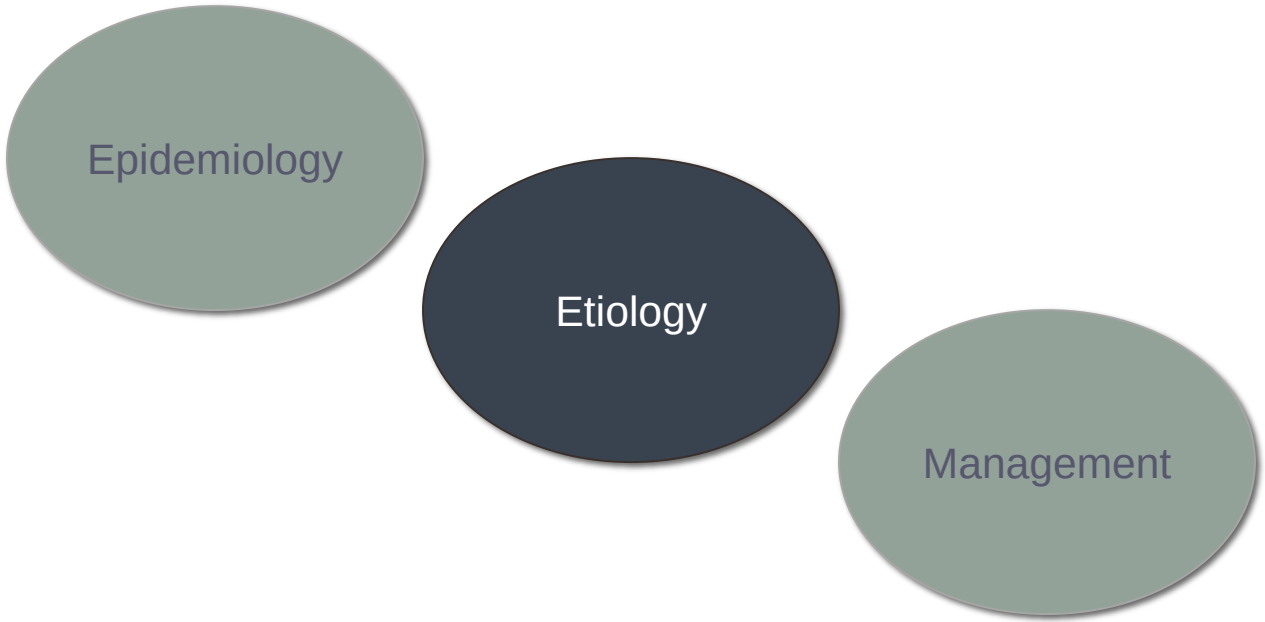
Incidence

- There is disagreement among experts regarding the frequency of acute exacerbation
  - In general, clinicians believe they are “common”
  - In general, clinical researchers believe they are “uncommon”

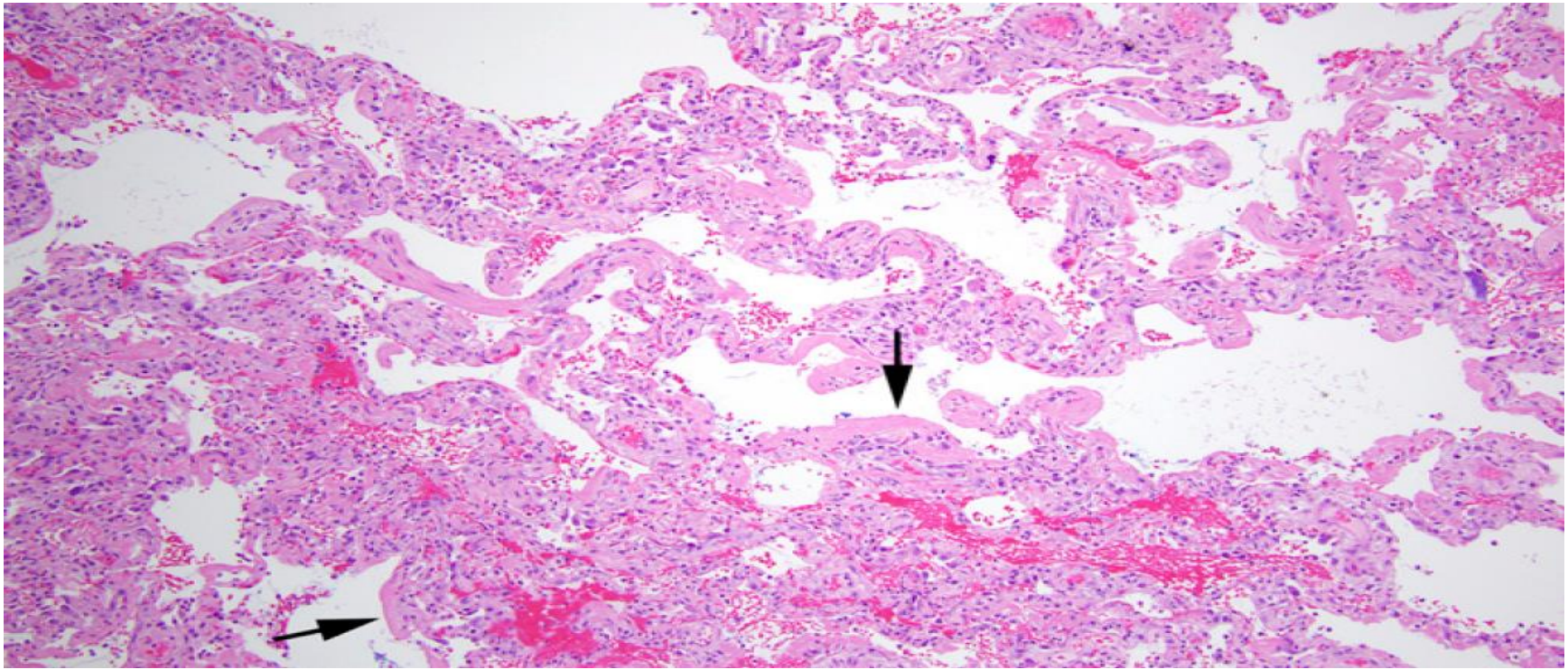
- Why is this?
  - Differences in disease severity
  - Involvement in clinical care
  - (Adherence to clinical criteria)



Collard Resp Res 2013;14:73


Epidemiology
Etiology
Management

Pathology shows acute lung injury



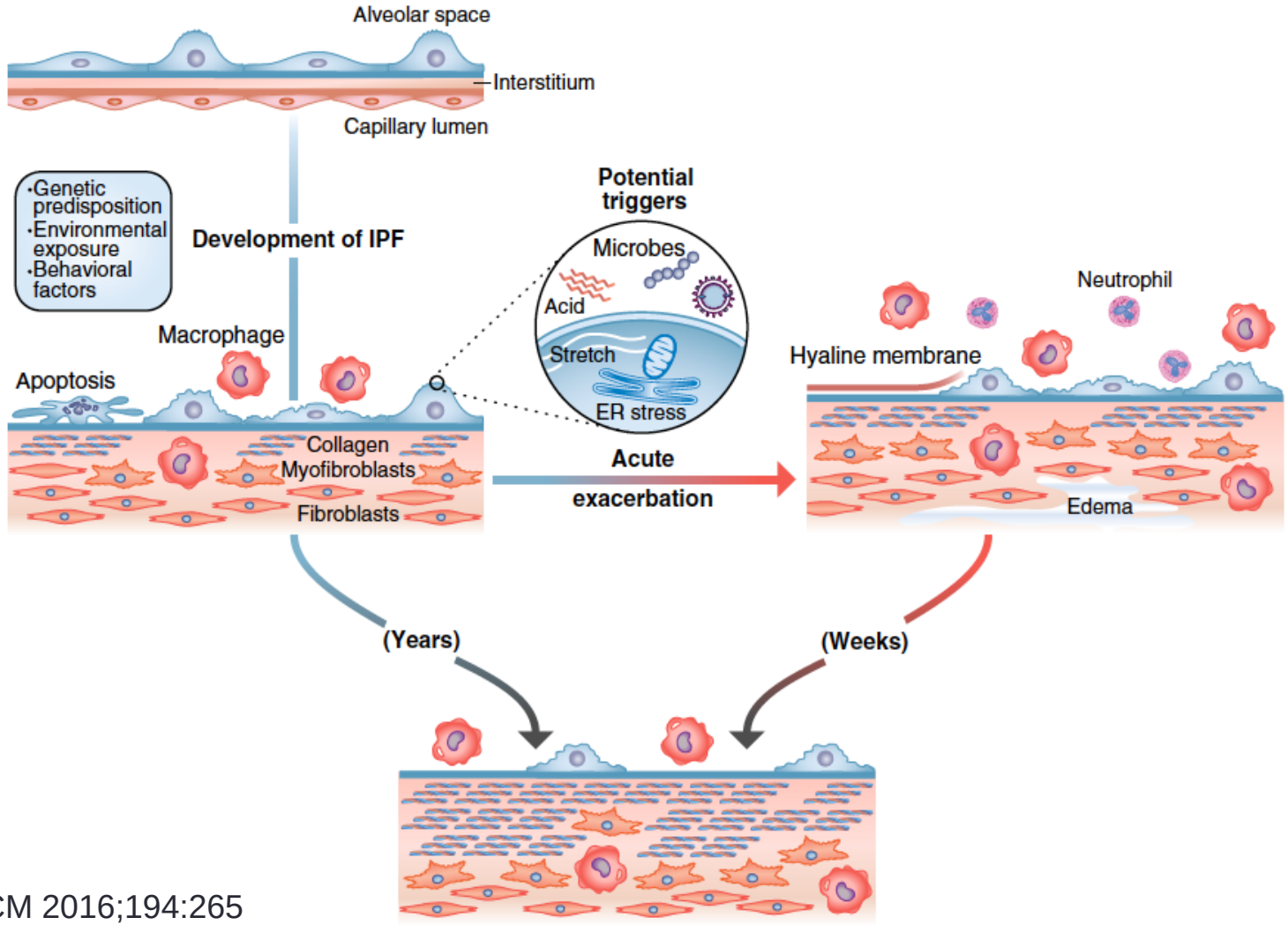
Collard AJRCCM 2007;176:636

Central question

"Do acute exacerbations of IPF represent a distinct pathobiological manifestation of the primary disease process or are they caused by occult triggers such as infection or aspiration?"

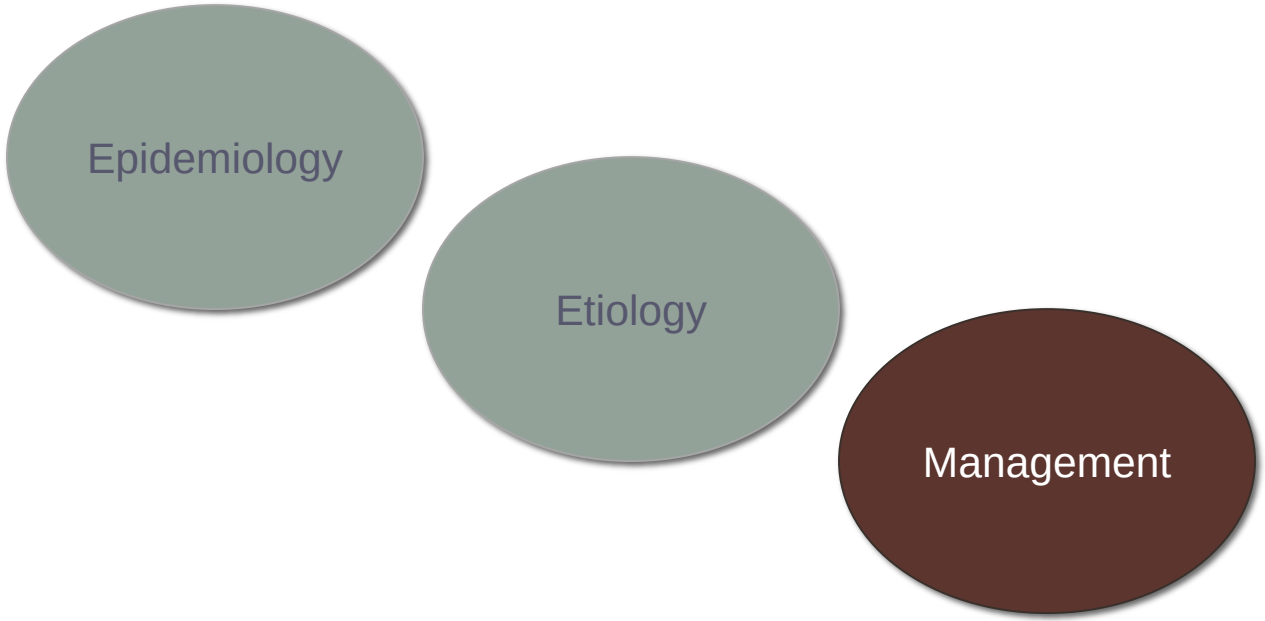
Collard et al. AJRCCM 2007;176:636

- Infection
- Aspiration
- Ambient pollution
- Surgery/stretch
- Medication



Collard AJRCCM 2016;194:265

What have we learned?



ATS/ERS/JRS/ALAT IPF Guidelines

- There are two management recommendations relevant to acute exacerbation of IPF made in this document

Intervention	Recommendation	Comments
Corticosteroids	**Yes (weak*)**	High value placed on anecdotal reports of benefit and the high mortality of acute exacerbation.
Mechanical ventilation	**No (weak*)**	A value-laden decision that is best made by the patient, clinician, and family ahead of time based on a firm understanding of the patient's goals of care.

* A weak recommendation applies majority of patients, but will not apply to some based on their values and preferences.

Raghu AJRCCM 2011;183:788

Proposed treatments

- Corticosteroid
- Cyclophosphamide
- Cyclosporine*
- Polymixin B column
- Plasma Ex/Rituximab *
- Tacrolimus *
- Thrombomodulin *

There are no published randomized, controlled trials.

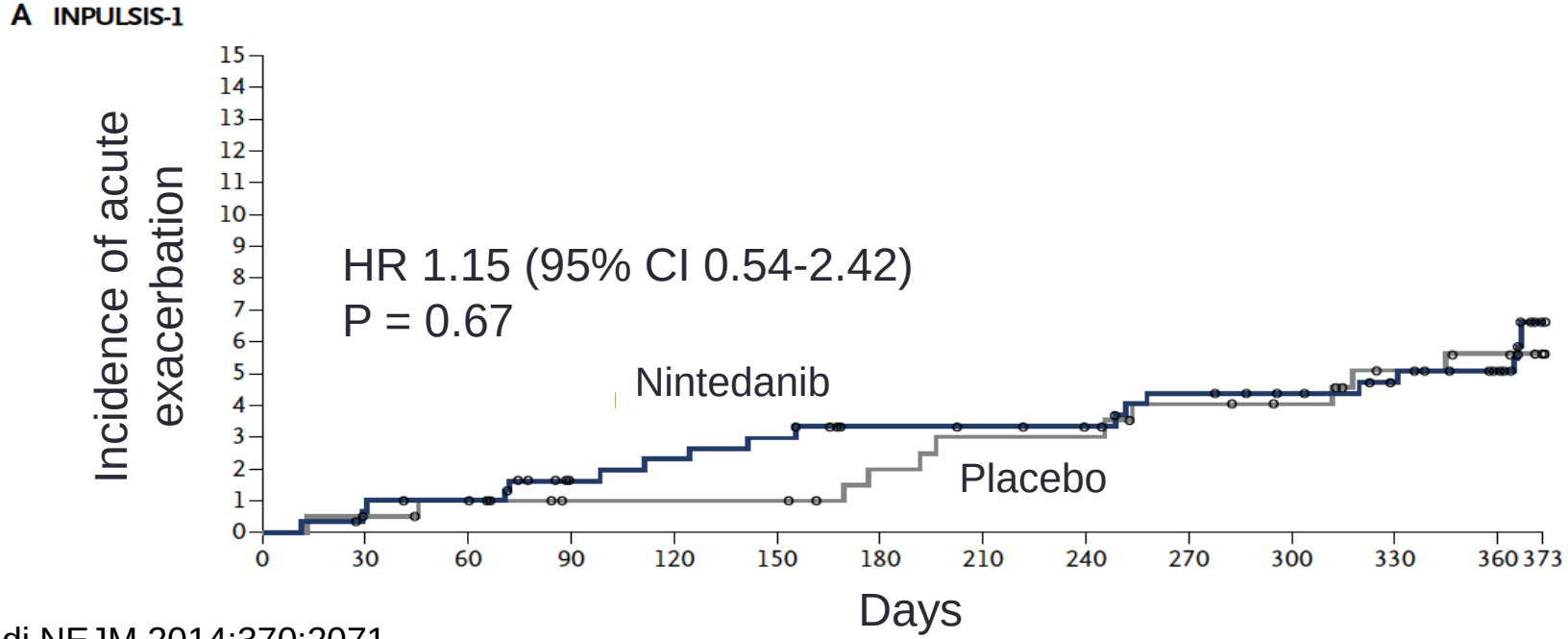
- * = small, controlled cohort studies published for these treatments.
- Other treatments have no published studies.

Prevention

- Nintedanib
- Pirfenidone
- Anti-acid therapy

Prevention

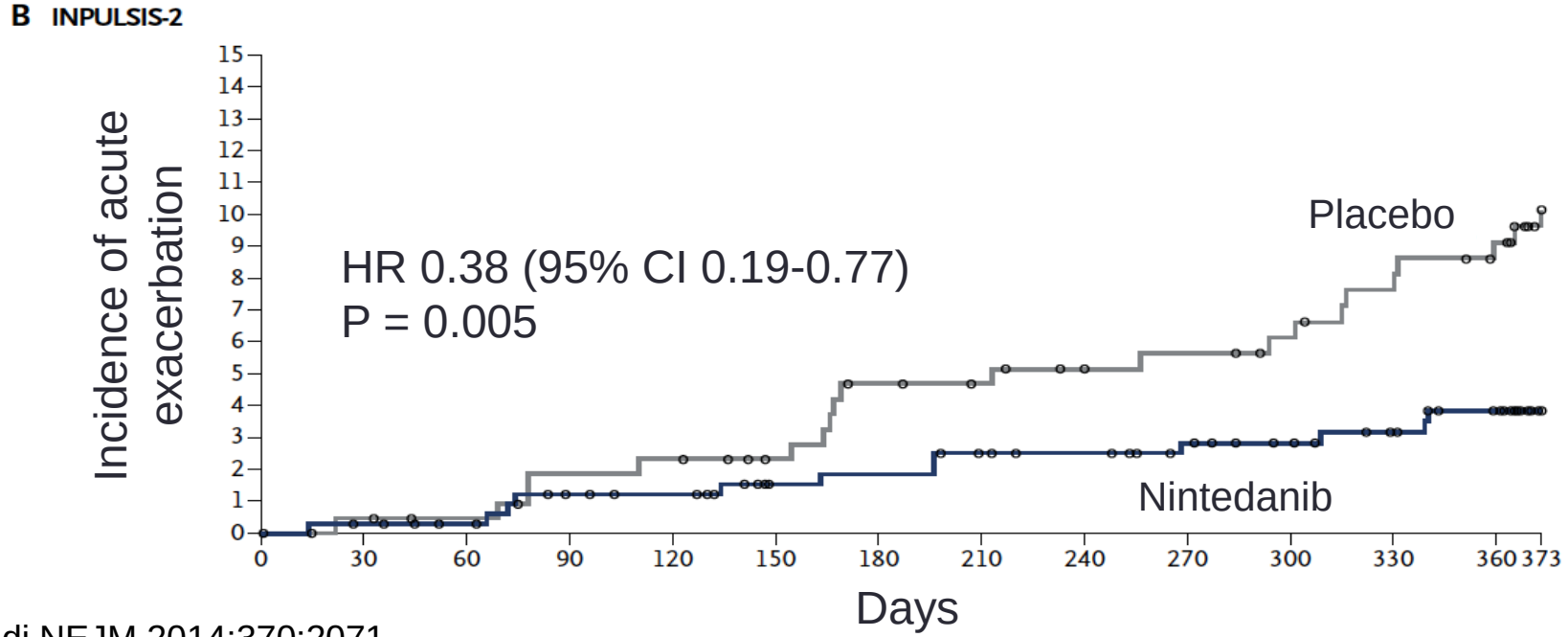
- Nintedanib



Richeldi NEJM 2014;370:2071

Prevention

- Nintedanib



Richeldi NEJM 2014;370:2071

Prevention

- Nintedanib

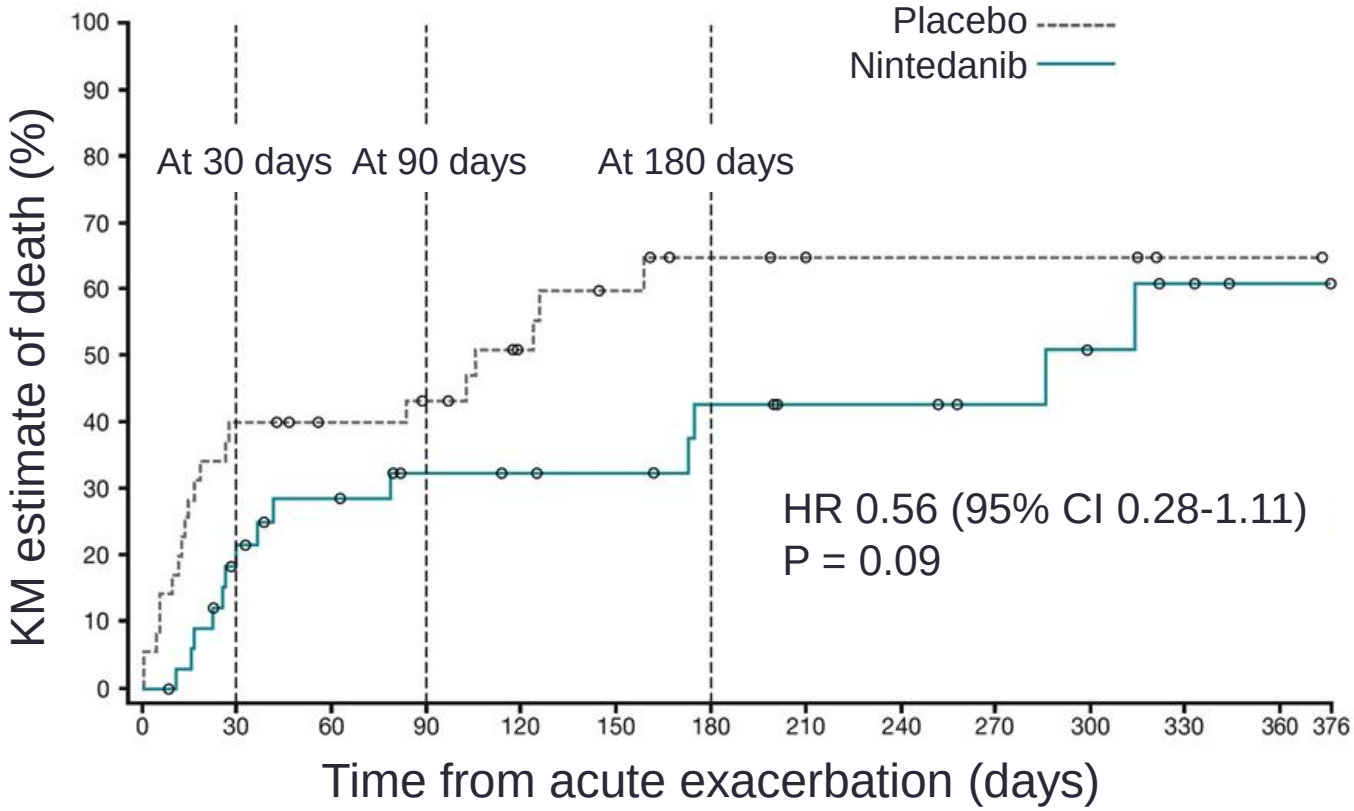
Table 3. Mortality Following Acute Exacerbation

	Patients with investigator-reported acute exacerbations		Patients with events adjudicated as confirmed or suspected acute exacerbations*		Patients with all events adjudicated as not acute exacerbations*	
	Nintedanib (n=34)	Placebo (n=35)	Nintedanib (n=14)	Placebo (n=25)	Nintedanib (n=23)	Placebo (n=13)
Mortality rate†						
30-day	7 (20·6)	14 (40·0)	3 (21·4)	9 (36·0)	4 (17·4)	5 (38·5)
90-day	10 (29·4)	15 (42·9)	5 (35·7)	12 (48·0)	6 (26·1)	7 (53·9)
180-day	12 (35·3)	20 (57·1)	6 (42·9)	15 (60·0)	7 (30·4)	7 (53·9)

Collard ERJ in press

Prevention

- Nintedanib



Collard ERJ in press

Prevention

- Pirfenidone

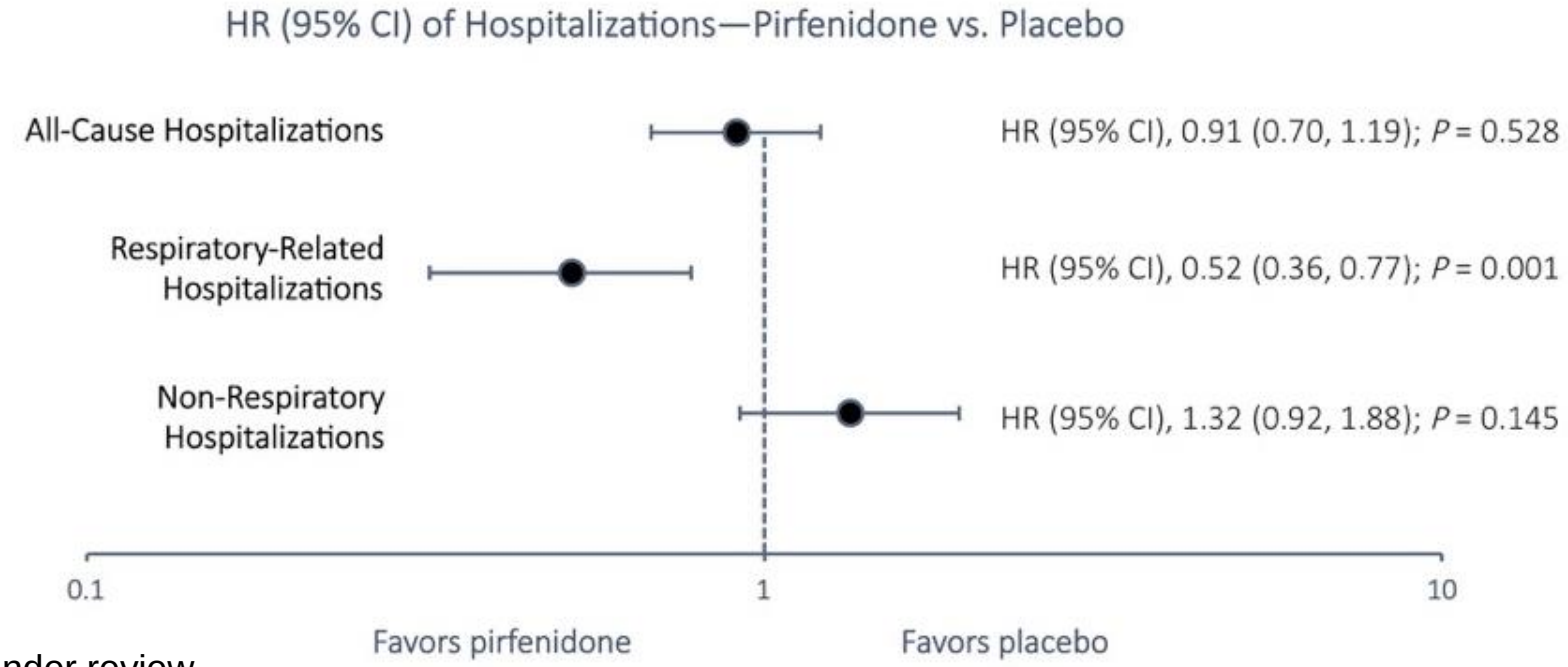
Table 2. Non-elective hospitalization events by type (all-cause, respiratory-related, and non-respiratory related) by treatment group

	All-Cause Hospitalizations		Respiratory Hospitalizations		Non-Respiratory Hospitalizations	
	Pirfenidone (N=623)	Placebo (N=624)	Pirfenidone (N=623)	Placebo (N=624)	Pirfenidone (N=623)	Placebo (N=624)
Total Events, n	139	151	54	87	85	64
Patients with ≥1 event, n (%)	106 (17)	115 (18)	41 (7)	74 (12)	70 (11)	54 (9)

Ley, Manuscript under review

Prevention

- Pirfenidone



Ley, Manuscript under review

ACUTE EXACERBATION

Is it time for a revised definition?

An argument for revision

- The paradigm of acute exacerbations as triggered events (rather than intrinsic disease worsening) is supported by both indirect and direct evidence.
  - DAD, the histopathlogic hallmark of acute exacerbation, is overwhelmingly caused by triggers.
  - Some acute exacerbations have been associated with potential triggers (e.g. viral infection).

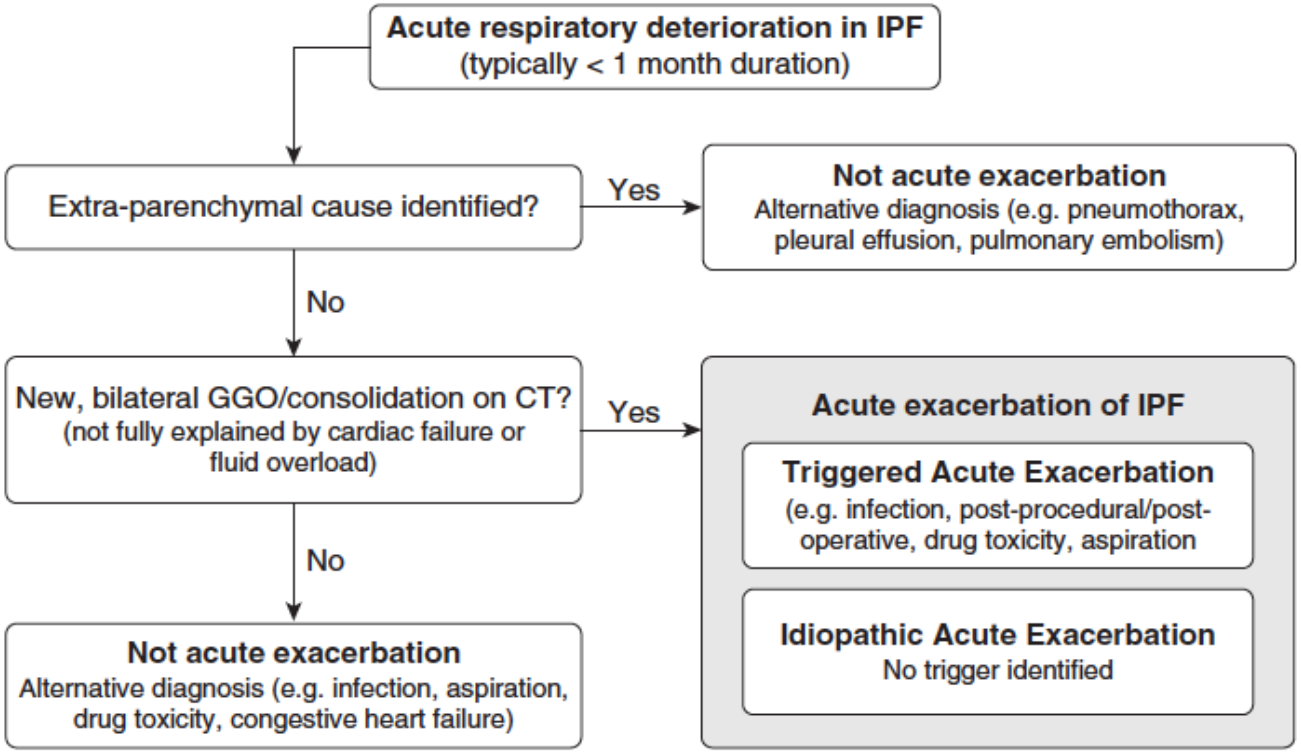
- The current definition has proven challenging for clinicians and clinical researchers.

Proposed revision

Current	Revised
An acute, clinically significant respiratory deterioration…	***An acute, clinically significant, respiratory deterioration…***
… of unidentifiable cause.	***…characterized by evidence of new widespread alveolar abnormality.***

Collard AJRCCM 2016;194:265

Proposed diagnostic framework



Collard AJRCCM 2016;194:265

Moving forward

- A revised definition for acute exacerbation should provide a simpler, more evidence-based platform for research.
  - Idiopathic acute exacerbations may still prove pathobiologically distinct and clinically important!
  - Research into the pathobiology/mechanism of acute exacerbation is greatly needed.
  - Randomized, controlled trials of therapies for acute exacerbation should be performed.

Thank you for listening!

Trigger = infection

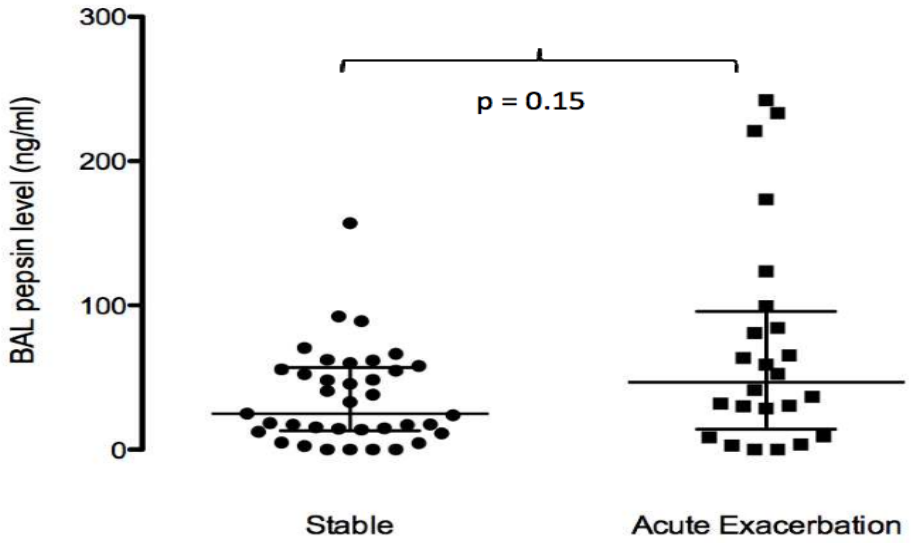
- A common respiratory virus was detected by deep sequencing in 9% of acute exacerbation BAL samples

Virus	Acute Exacerbation n = 43	Stable IPF n = 40	P value
Rhinovirus	2 (5%)	0 (0%)	0.49
Coronavirus	1 (2%)	0 (0%)	1.0
Parainfluenza	1 (2%)	0 (0%)	1.0
Adenovirus	0 (0%)	0 (0%)	--
Enterovirus	0 (0%)	0 (0%)	--
Influenza	0 (0%)	0 (0%)	--
Metapneumovirus	0 (0%)	0 (0%)	--
RSV	0 (0%)	0 (0%)	--

Wootton AJRCCM 2011;183:1698

Trigger = aspiration

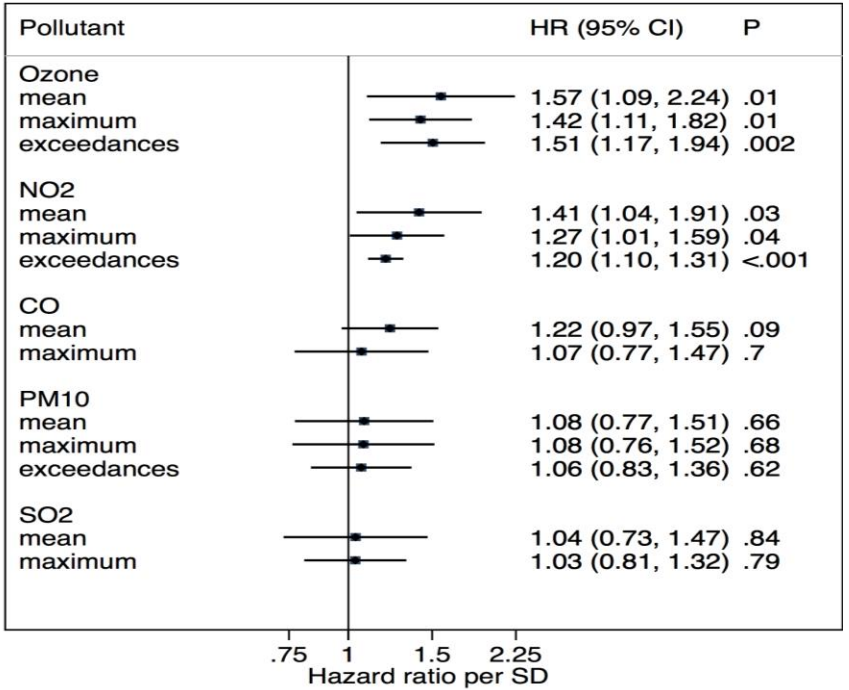
- Eight of 24 (33%) patients with acute exacerbation had elevated pepsin levels in their BAL compared to stable IPF patients



Lee ERJ 2012;39:352

Trigger = ambient pollution

- Recent ozone and nitrogen dioxide (NO2) exposure was associated with an increased risk of acute exacerbation



Johannson ERJ 2014;43:1124