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REVIEW

Terms and Definitions Used to Describe Recurrence, Treatment Failure and Recovery of Acute Exacerbations of COPD: A Systematic Review of Observational Studies

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Introduction: Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are important clinical events, with many patients experiencing multiple AECOPDs annually. The terms used in the literature to define recurring AECOPD events are inconsistent and may impact the ability to describe the true burden of these events. We undertook a systematic review to identify and summarize terms and definitions used in observational studies to describe AECOPD-related events occurring after an initial AECOPD (hereafter "subsequent AECOPD").

Methods: PubMed was searched (2000–2019) for observational studies on subsequent AECOPD events using broad search strings for "COPD", "exacerbation", and "subsequent exacerbation events". Only English-language studies were included. Small studies (n<50) and studies focusing on hospital re-admission only were excluded. Extracted data were analyzed descriptively to generate a narrative summary, using a thematic approach to group studies utilizing similar terms for subsequent AECOPD.

Results: Forty-seven studies were included. No single, distinct terms or definitions were used to define and identify multiple occurrences of AECOPDs, though most (46) studies used one or more of four clustered terms and definitions: reapse (n = 13), recurrence/re-exacerbation (n = 11), treatment failure (n = 12) and non-recovery/time to recovery (n = 16). Heterogeneity was observed within and between the four clusters with respect to study setting, starting point for observing subsequent AECOPDs, time frame to identify a subsequent AECOPD (except for studies using "time to recovery"), and basis for identifying a subsequent exacerbation.

Conclusion: Our review demonstrates that subsequent AECOPDs (including events such as relapse, recurrence/re-exacerbation, treatment failure, non-recovery/time to recovery) are ill-defined in the observational study literature, emphasizing the need to reach consensus on precise and objective definitions (for example, when one AECOPD ends and another begins). Use of standardized terminology and definitions may aid comparability between, and synthesis of, studies, thus improving the understanding of the natural history and burden of exacerbations in COPD patients.

Keywords: chronic obstructive pulmonary disease, recurrence, exacerbation, review

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Introduction

Chronic obstructive pulmonary disease (COPD) is the 3rd leading cause of mortality worldwide[1] and a significant cause of morbidity.[2] Acute exacerbations of COPD (AECOPDs) are important clinical events and contribute significantly to overall

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disease burden and mortality.[3] AECOPDs are generally defined as an acute, and sustained, worsening of respiratory symptoms requiring additional treatment, including hospitalization when severe.[4–6] Approximately 50% of COPD patients experience at least one AECOPD event each year, with exacerbations occurring across all stages of disease severity.[7,8] Frequent AECOPD events may increase a patient's risk of mortality,[9] and decrease their lung function[10–12] and quality of life.[13] Severe AECOPDs pose a financial burden, with AECOPD hospitalizations accounting for up to 70% of COPD-related healthcare expenditures.[14–16]

The European Respiratory Society/American Thoracic Society guidelines on COPD management of exacerbations proposed in 2017 state that exacerbations are defined as "episodes of increasing respiratory symptoms, particularly dyspnea, cough and sputum production, and increased sputum purulence".[17] In clinical trials and observational studies, AECOPDs tend to be defined based on symptoms (eg, following the classic Anthonisen classification),[18] healthcare utilization (eg, prescriptions for AECOPD treatment, management in hospital), or both.[19] Identification of symptoms suggestive of AECOPDs may be prospectively recorded in patient daily diaries,[20] or retrospectively recalled in patient interviews. Alternatively, evidence of healthcare resource utilization (HCRU) for AECOPD may be identified using records in an electronic health records or administrative claims database. A prospective analysis of exacerbations identified by either symptoms or HCRU demonstrated a higher mean rate of exacerbations using the HCRU definition and showed limited agreement between HCRU and symptom-based exacerbations, thus complicating the evaluation of exacerbations in published studies.[21]

Despite the existence of guidelines and efforts to clarify best practice, there is no international consensus or standardized definition of how the start and end dates for exacerbations should be defined. For example, discharge from hospital for treatment of an AECOPD is often used to define the end of an exacerbation in observational studies; however, patients are still likely to be experiencing exacerbation symptoms after discharge, with exacerbation symptoms typically lasting around a week and some lasting as long as 8 weeks or more.[22] Whilst algorithms have been defined and validated to identify AECOPD in electronic health records,[23] there remains, however, considerable heterogeneity amongst the definitions for AECOPD.[19]

In addition to challenges that exist with defining when an AECOPD event starts and ends, there are further challenges in defining recurring AECOPD events (ie, when does the initial AECOPD event end and another start), as well as AECOPD recovery and treatment failure. Collectively, we refer to these AECOPD-related events occurring after an initial AECOPD as "subsequent AECOPD events". Differences in study designs, definitions, and how AECOPD was ascertained yield different estimates of re-exacerbation risk within discrete time periods. There is recognition within the research community that a lack of standardized, consistently used definition for exacerbations hampers efforts to assess new therapeutic approaches for AECOPD treatment.[24,25] As a first step in obtaining external consensus on how subsequent mild, moderate or severe AECOPD events should be defined, our primary objective was to conduct a systematic review to identify and critically summarize the terms and definitions used in observational studies to describe recurrence, treatment failure and recovery of AECOPD. In order to demonstrate the impact on potential inconsistency of definitions for subsequent AECOPD events, a secondary objective was to report the frequency of recurrent AECOPD events, in addition to non-recovery and treatment failure events.

Methods

We performed a systematic review of observational studies reported in the literature. PubMed was searched for relevant studies published between 1 January 2000 and 31 December 2019. Search strings for terms relating to "disease", "exacerbation", and "subsequent exacerbation events" were combined using an AND operator (see Supplement for details). The search was limited to articles with available abstracts and published in the English language; there was no restriction on the geographical scope.

Articles describing subsequent AECOPD events (eg, recurrence, treatment failure or recovery) in relation to an initial or index AECOPD event were included, with screening performed in two stages. In Stage 1, titles and abstracts were reviewed for the following exclusion criteria: study not presenting original observational research (clinical trials, randomized clinical trials, narrative reviews, letters, case reports); study reporting hospital readmission only; no outcomes of interest (ie, subsequent AECOPD); articles did not answer review objective. In Stage 2, the full text of articles identified in Stage 1 for potential inclusion were reviewed for all the exclusion

criteria from Stage 1, plus the following additional exclusion criteria: study not describing subsequent AECOPD events in relation to an index AECOPD, no outcome of interest, hospital readmission only study including chronic bronchitis patients only, sample size <50, review article. Disagreements were resolved at both stages by consensus or arbitration with an additional reviewer. As a minimum, 1 person screened the titles/abstracts and performed the full text selection, with another extracting the data. Each step was cross-checked by an independent reviewer. Study investigators were not contacted.

Data from the included studies were extracted into evidence tables summarizing study design and population, definition and terminology for subsequent AECOPD event(s), time point from which subsequent AECOPD events were observed (eg, hospital discharge), and length of follow-up to observe subsequent AECOPD events. Where available, the proportion of patients experiencing a subsequent AECOPD event, or the mean time to subsequent AECOPD event was extracted. Data extraction was cross-checked by multiple researchers. Quality of the included studies was assessed broadly with a focus on the completeness of the subsequent AECOPD definition. No studies were excluded from the review based on quality assessment. Extracted data were analyzed descriptively to generate a narrative summary. A thematic approach was used to group studies utilizing similar terms for subsequent AECOPD.

This comprehensive review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[26] for systematic reviews except for two points: the review was not registered and no formal assessment of the risk of bias or quality of the evidence for included studies was performed, however, this was informally assessed.

Results

At Stage 1 (title and abstract review), 1291 articles (of 1427 identified) were excluded, with 136 articles proceeding to Stage 2 screening (full text review). At Stage 2, 89 articles were excluded, leaving 47 selected for data extraction. The number of articles identified, screened, assessed for eligibility and then included in the review are presented in Figure 1. A description of 46 of the included articles is in Tables 1–4 with further description of all 47 articles in the Supplement.

Terminology

Terminology describing subsequent AECOPD was clustered into four broad groups: relapse, recurrence/re-exacerbation, treatment failure, non-recovery/time to recovery (Tables 1–5). The majority (46) of included studies used these terms and definitions, with some studies using two or more of the four terminology groups.[8,27,28] A single study (Matkovic [2012]) used the term adverse outcome, which had a definition similar to definitions for treatment failure in other studies, but was not grouped with the other studies on the basis that the term differed from the four common terms.[29]

Relapse

Exacerbation relapse was a term used by 13 articles and was typically defined as a return to the emergency department (ED) or another physician visit for worsening symptoms and typically not differentiated from recurrence or re-exacerbation (Table 1).[27,28,30–40] Only relapses of moderate or severe exacerbations were reported. The most common study setting where the term relapse was used was the ED (n = 6), followed by outpatient clinics (n = 3), hospital (n = 2), and then primary care (n = 1). One study was set in both the hospital and ED.[38] Almost all studies calculated the proportion of patients with relapse using the number of patients as the denominator: four studies used exacerbations or patient visits as the denominator.[28,31,32,40] The timeframe for observing relapse events ranged from five days to one month, with fourteen days being the most common (Figure 2A). The proportion of patients with exacerbation relapse during the timeframe ranged from 7.4% at/before 20 days to 34% at/before one month with no clear trend observed over time.

Recurrence/Re-Exacerbation

The terms exacerbation recurrence or re-exacerbation were used in 11 articles (Table 2).[28,41–50] Most studies defined recurrence or re-exacerbation as a worsening of symptoms (n = 3), subsequent prescription of oral corticosteroids or antibiotics (n = 2), or as a composite outcome including treatment or readmission for AECOPD following an initial AECOPD (n = 3). Only four studies specified that recovery from initial AECOPD was required prior to subsequent AECOPD and only recurrence/re-exacerbation of moderate or severe exacerbations were reported. The most common study setting was the hospital (n = 7), followed by outpatient clinics (n = 2), and primary care (n = 1). One study included both hospital inpatient and outpatient

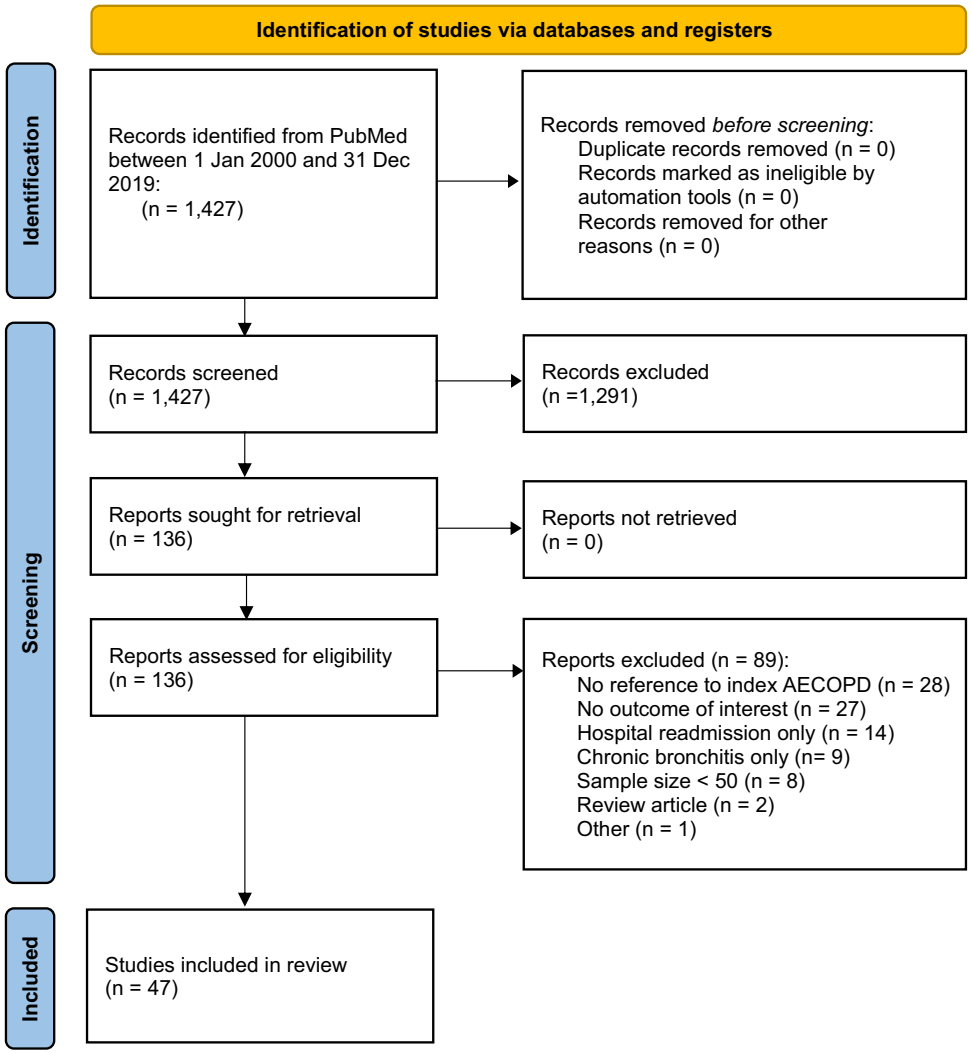

Figure 1 PRISMA* flow diagram of included and excluded articles. *Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71.[26]
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PRISMA, The Preferred Reporting Items for Systematic reviews and Meta-Analyses.

participants.[50] The timeframe for recurrence or re-exacerbation definitions reporting proportions ranged from one month to 12 months, with either hospital discharge as the initial time point for follow-up (which may or may not be the point at which a patient has "recovered") (n = 6) or measured following consecutive days free of recorded symptoms (n = 1). The proportion of patients with recurrence/re-exacerbation ranged from 7.4% at/before one month to 88.8% at/before one year, in the same study. Figure 2B shows a trend between length of follow-up and the proportion of patients with a recurrence/re-exacerbation event; however, variability is still seen among studies using the same starting point for follow-up (eg, by 90 days, the proportion of patients with an event following hospital discharge ranged from 25% to 49%).

Treatment Failure

Treatment failure was a term used by 12 articles and was defined as a composite of absence of symptom resolution (n = 2), antibiotic or oral corticosteroid prescription or change in medication (n = 3), hospital readmission (n = 7), increased mechanical ventilator support (n = 5), and/or death (n = 7).[51–62] One study defined treatment failure as failure to return to baseline or need for a new treatment medication.[57] Treatment failure was a term only used for moderate or severe exacerbations. The most common study setting for treatment failure was the hospital (n = 7), with other studies set in outpatient clinics (n = 3), primary care (n = 1), and home care (n = 1). The timeframe for observing treatment failure ranged from two days from hospital

Table 1 Characteristics of Studies Observing Relapse Events Following an Exacerbation

Author, Year	Relapse Definition	N[a]	Country, Study	Study Setting	Time Point From Which Relapse is Measured	Proportion Relapsed [Time Frame, (Days)][b]
Aaron 2002[30]	Re-visit to ED or other physician for worsening symptoms	66	Canada	ED	Initial ED visit	26% (10)
Adams 2000[31]	Return visit to ED	362 visits	USA	ED	Initial ED visit	22% (14)
Cydulka 2003[27]	Patient report of same or worsening condition since last ED visit	185	USA and Canada, MARC	ED	Initial ED visit	14% (14)
Domenech 2013[32]	New exacerbation by pneumococci with different serotype than index exacerbation	116 exacerbations	Spain	Hospital	Not reported	69.8%[c]
Durmaz 2015[34]	Symptoms within 5 days of index exacerbation	196	Turkey	ED	Initial ED visit	27.6% (14)
Durmaz 2015[33]	Re-visit to ED for worsening symptoms	92	Turkey	ED	Initial ED visit	30% (14)
Hurst 2009[28]	Symptoms within 5 days of index exacerbation	410 exacerbations	UK, London COPD Cohort	Outpatient	Remission of symptoms	11% (5)
Kim 2004[35]	Re-visit to ED or clinic	140	USA and Canada, MARC	ED	Initial ED visit	17% (14)
Minov 2018[36]	Worsening cough, expectoration, and shortness of breath	54	Macedonia	Outpatient	Remission of symptoms	7.4% (20)
Miravitlles 2001[37]	Unscheduled visit leading to change in drug prescription, an ED visit, or hospital admission	2414	Spain	Primary care	Initial primary care visit	21% (1 mo)
Miravitlles 2003[38]	Unscheduled office visit or hospitalization for persistent or worsening symptoms	441	Spain	Outpatient clinic	Following initial exacerbation Initiation of antibiotic therapy	34% (1 mo) Mean time to relapse: 4.6 (SD 3.3)
Stiell 2018[39]	Return to ED for any related problem, with or without admission to hospital	1415	Canada	Hospital and ED	Unclear if hospital discharge or admission	ED: 21.8% (14 d)[d] ED with admission: 8.3% (14 d)[e]
Vondracek 2006[40]	Hospital admission, ED visit, or clinic visit	80 admissions	USA	Hospital	Discharge	28% (30)

Notes: [a]N indicates number of patients unless otherwise specified; [b]Days unless otherwise specified; [c]Not reported in Figure 1A because no time horizon included; [d]Defined as return to ED for any related problem; [e]Defined as return to ED for any related problem followed by admission to hospital.

Abbreviations: COPD, chronic obstructive pulmonary disease; d, days; ED, emergency department; MARC, Medication Adherence Research in COPD Patients; mo, months; SD, standard deviation; UK, United Kingdom; USA, United States of America.

Table 2 Characteristics of Studies Observing Recurrence or Re-Exacerbation Events Following an Exacerbation

Author, Year	Re-Exacerbation or Recurrence Definition	N[a]	Country, Study	Setting	Time Point From Which Re-Exacerbation or Recurrence is Measured	Proportion with Re-Exacerbation or Recurrence [Time Frame, (Days)][b]
Bartziokas 2014[41]	The need for antibiotics and/or OCS, visits to ED, and/or hospitalizations	314	Greece	Hospital	Discharge[c]	High uric acid 50% (3 mo), 80% (6 mo) Low uric acid 15% (3 mo), 60% (6 mo)
Bathoorn 2017[42]	Prescription of subsequent course of corticosteroids within 60 days of first course	1558 exacerbations	The Netherlands	Primary care	First course of prescribed corticosteroids[d]	28% (60)
Chang 2014[43]	Re-exacerbation after symptoms from initial exacerbation returned to pre-exacerbation level	135	China	Hospital	Discharge	18.5% (56)
Cushen 2016[44]	Requiring antibiotics and/or steroid therapy	62	Ireland	Hospital	Discharge	14.5% (14)
Hu 2019[45]	Worsening respiratory symptoms for ≥2 consecutive days requiring intervention or medication changes after sustained relief from last exacerbation of ≥14 days	686	China	Hospital	Discharge	15% (30)
Hurst 2009[28]	New exacerbation after symptom free for 5 days within 8 weeks of previous exacerbation	410 exacerbations	UK, London COPD Cohort	Outpatient	Remission of symptoms[e]	27.4% (56) Median days to re-exacerbation or recurrence: 5 [Q1, Q3: 3, 8]
Johannesdottir 2013[46]	Inpatient readmission or re-visit, mechanical ventilation, or simultaneous antibiotics and steroid prescription	6240 exacerbations	Denmark	Hospital	Discharge	19.7% (30) 31.6% (60) 40.1% (90) 57.4% (180)
Liu 2015[47]	Sustained worsening of symptoms for ≥2 days requiring visit to doctor, ED, and/or antibiotics, corticosteroids, or both	176	China	Hospital	Discharge	48.9% (90)
Perera 2007[48]	New exacerbation after symptom recovery from index exacerbation	73	UK, London COPD Cohort	Outpatient	Onset of index exacerbation[f]	22% (50) Median days to re-exacerbation or recurrence: 9 [Q1, Q3: 4, 18]
Wang 2012[49]	Worsening cough, expectoration, and shortness of breath	136	China	Hospital	Discharge	7.4% (30) 25% (90) 55.6% (180) 88.2% (365)

(*Continued*)

Table 2 (Continued).

Author, Year	Re-Exacerbation or Recurrence Definition	N[a]	Country, Study	Setting	Time Point From Which Re-Exacerbation or Recurrence is Measured	Proportion with Re-Exacerbation or Recurrence [Time Frame, (Days)][b]
Yount 2019[50]	Sustained worsening of COPD symptoms beyond normal day-to-day variations with acute onset requiring change in regular medication, admission for COPD, and/or treatment with antibiotics or corticosteroids	85	USA	Hospital inpatients and outpatients	Enrollment into the study[g]	17.6% (84)

Notes: [a]N represents patients unless otherwise noted; [b]Days unless otherwise specified; [c]Patients were evaluated on admission and at discharge by the study investigators and were followed up for 1 year; [d]Unclear whether follow-up began at prescription start or end; [e]After 5 consecutive symptom-free days; [f]Not explicitly mentioned in article, but for other outcomes such as non-recovery the starting point is onset of index exacerbation; [g]Maximum of 3 days from start of treatment for patients recruited in outpatient setting and maximum of 6 days from treatment start for patients recruited in the inpatient setting.
Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; mo, months; OCS, oral corticosteroids; Q1, quartile 1; Q3, quartile 3; UK, United Kingdom; USA, United States of America.

admission[60] to ninety days from hospital discharge.[54] The proportion of patients with treatment failure ranged from 14.5% at/before seven days[51] to 36.8% at/before 90 days.[54] By 30 days (the most common timeframe), the proportion experiencing treatment failure ranged from 7.4% to 34.8%[55] – suggesting heterogeneity in the studies, potentially due to a range of definitions for treatment failure between studies.

Non-Recovery and Time to Recovery

The term non-recovery from an exacerbation was used as a definition for subsequent AECOPD events in 17 studies and was predominantly defined as either symptoms or peak expiratory flow not returning to baseline.[10,27,28,36,38,48,57,63–72] Eight studies using the term non-recovery were set within the London COPD cohort, which used patient diary cards to assess recovery. Four of the studies were conducted in outpatient clinics, and two in the ED. One study did not report setting. Four studies, three in the London COPD cohort and one in GIANT, reported both time to recovery and proportion of patients non-recovered by a certain number of days post index.[48,63,71,72]

Timeframes for non-recovery definitions ranged from eight days from an unclear start point[62] to three months from start of exacerbation.[72] The proportion of patients who met the criteria for non-recovery ranged from 8.3% at 99 days[72] to 25% at 35 days.[71] Thirteen articles reported mean or median time to recovery rather than (or in addition to) the proportion of patients recovering. Most of these studies were based in the London COPD cohort and conducted in an outpatient setting. Median time to recovery of symptoms in the London COPD studies ranged from 7 days (Q1, Q3: 4, 14 days)[71] to 10 days (Q1, Q3: 6, 18 days),[72] with similar median time to recovery of peak expiratory flow of 5 and 6 days (Q1, Q3: 0, 14 days and 1, 14 days).[71,72] One study reported mean time to "early" recovery (≤4 days) and to "late" recovery (≥8 days) of 3.1 days (SD: 0.9 days) and 102 days (SD: 2.5 days), respectively.[63] Overall, median recovery time ranged from 5 days[28] to 13 days[30] and mean recovery time ranged from 3 days[63] to 19 days.[66]

Six studies reported "time to recovery" only (ie, no proportions) in either an outpatient (n = 5) or cohort (n = 1) study setting, with recovery defined as improvement in symptoms. Two studies measured time from the initial patient visit, three measured time from onset of exacerbation, and one measured time from the last COPD exacerbation. One study presented total recovery time and treated recovery time,[69] and one study presented time to recovery stratified by chronic bronchitis status.[66] Mean time to recovery ranged from 6.3 days (SD 3.1 days)[68] to 13.3 days (SD: 13.3 days).[69] Median time to recovery ranged from 7 days (Q1, Q3: 0, 12 days)[67] to 13 days (Q1, Q3: 7, 29 days).[73]

Table 3 Characteristics of Studies Observing Treatment Failure Following an Exacerbation

Author, Year	Treatment Failure Definition	N[a]	Country, Dataset	Setting	Time Point From Which Treatment Failure is Measured	Proportion with Treatment Failure [Time Frame, (Days)][b]
Beauchesne 2008[51]	Prolonged use of antibiotics, ED visit, or hospitalization	1180 exacerbations	Canada	Home care program	Initiation of antibiotic treatment	29.5% (30)
Crisafulli 2016[52]	Need for NIMV, ICU admission, new course of antibiotics, or death	110	Spain	Hospital	Day 2 of admission	14.5% (7)
Dewan 2000[53]	Readmission or re-visit requiring a change of antibiotic	107	USA	Outpatient	Commencement of initial treatment	26% (28)
Garcia-Sidro 2015[54]	Exacerbation with or without readmission, or death	106	Spain	Hospital	Discharge	36.8% (90)
Gaude 2015[55]	Return visit requiring change of antibiotic or hospitalization	115	India	Hospital	Discharge	34.8% (28)
Lindenauer 2010[56]	Mechanical ventilation after second hospital day, death during hospitalization, or readmission	79,985	USA, Premier Perspective	Hospital	Discharge	10.8% (30)
Miravitlles 2005[57]	Failure to return to baseline or need for new treatment or medication	1147	Spain	Primary care	Initial visit	15.1% (10)
Miravitlles 2011[58]	Absence of sign/symptom resolution, worsening of signs/symptoms or death	346	Spain	Outpatients	Initial visit	28.2% (30)
Miravitlles 2013[59]	Incomplete resolution, persistence, or worsening of symptoms requiring new course of antibiotics and/or OCS or hospitalization	260	Spain	Outpatients	Initial visit	13.5% (28) Mean days to treatment failure: 7 [SD 4.6]
Planquette 2015[60]	Increased mechanical ventilator support, initiation of OCS, or death	111	France	Hospital (ICU)	Admission	21.6% (2)
Rothberg 2010[61]	Initiation of hospital mechanical ventilation, in-hospital death, or readmission	19,608	USA, Premier Perspective	Hospital	Day 2 of admission[c], or discharge	7.7% (30)
Rothberg 2010[62]	Initiation of hospital mechanical ventilation, in-hospital death, or readmission	84,621	USA, Premier Perspective	Hospital	Day 2 of admission[c], or discharge	10.2% (30)

Notes: [a]N represents patients unless otherwise noted; [b]Days unless otherwise specified; [c]Starting point for treatment failure defined as initiation of mechanical ventilation at day 2 of hospital admission.

Abbreviations: ICU, intensive care unit; NIMV, non-invasive mechanical ventilation; OCS, oral corticosteroids; SD, standard deviation; USA, United States of America.

Discussion

In our systematic review, we found no single, distinct terms or definitions were used to define subsequent AECOPD events in the observational study literature, though most studies used one of four clustered terms and definitions: relapse, recurrence/re-exacerbation, treatment failure and non-recovery/time to recovery. Both heterogeneity and similarities were observed among terminologies of subsequent AECOPD, and in the time frames and the settings used to assess these subsequent AECOPD events. Despite some similarities, the heterogeneity we observed may hamper comparability and synthesis of these studies.

Table 4 Characteristics of Studies Observing Non-Recovery or Time to Recovery Events Following an Exacerbation

Author, Year	Non-Recovery or Recovery Definition	N[a]	Country/ Study	Setting	Time Point From Which Non-Recovery is Measured	Proportion Not Recovered [Time Frame, (Days)][b]
Anzueto 2012[63]	Non-Recovery: Acute increase in 1 or more symptoms (dyspnea, sputum volume, sputum purulence) Recovery: Clinician assessment that patient is free of symptoms	40,435	GIANT[c]	Not reported	Unclear	15% not recovered (8) Mean time to recovery among those with late and early recovery: 10.2 [SD 2.5]; 3.1 [SD 0.9][d]
Cydulka 2003[27]	Non-Recovery: Symptoms at telephone interview for ≥24 hours or condition same or worsened since last ED visit	186	MARC[e]	ED	Presenting to ED	40% not recovered (14)
Donaldson 2003[10]	Non-Recovery: PEF or symptom score below baseline with symptoms recorded on diary card	1111 exacerbations	UK, London COPD Cohort	Outpatient	Onset of index exacerbation	Symptom recovery: 9.6% not recovered (35) PEF recovery: 11.6% not recovered (35)
Donaldson 2015[72]	Non-Recovery: Worsening symptoms or change in medication required or PEF below baseline Time to recovery: First of 2 consecutive symptom-free days or PEF returned to baseline	3087 exacerbations	UK, London COPD Cohort	Outpatient	Onset of index exacerbation	Symptom recovery: 3.1% not recovered (99 d) Days to recovery: Mean: 14.7 [SD: 14.2] Median: 10 [Q1, Q3: 6, 18] PEF recovery: 7.3% not recovered (99) Days to recovery: Mean: 10.3 [SD 15] Median: 5 [Q1, Q3: 0, 14] (0, 14 d)
Perera 2007[48]	Non-Recovery: Total symptom score not returned to baseline Time to recovery: time from onset of exacerbation to day on which a 3-day moving average of symptom score returned to baseline	73	UK, London COPD Cohort	Outpatient	Onset of index exacerbation	23% not recovered (35) Median days to recovery: 9 [Q1, Q3: 4, 18]
Seemungal 2000[71]	Non-Recovery: PEF or symptoms not returning to baseline Time to recovery: symptoms or PEF returned to baseline	504 exacerbations	UK, London COPD Cohort	Outpatient	Onset of index exacerbation	Symptom recovery: 13.9% (35) 9.1% (91) Median days to recovery: 7 (Q1, Q3: 4, 14) PEF recovery: 24.8% (35) 19.8% (91) Median days to recovery: 6 (Q1, Q3; 1, 14)
Tsai 2009[70]	Non-Recovery: Patient report of COPD status as much worse, a little worse, or about the same during telephone interview	330	MARC[e]	ED	Presenting to ED	18% (14)

(*Continued*)

Table 4 (Continued).

Author, Year	Non-Recovery or Recovery Definition	N[a]	Country/ Study	Setting	Time Point From Which Non-Recovery is Measured	Proportion Not Recovered [Time Frame, (Days)][b]
Aaron 2012[73]	Time to Recovery: first date of 5 consecutive days where self-reported symptoms return to usual baseline	1995 exacerbations	UK, London COPD Cohort	Outpatient	Onset of index exacerbation	Sudden onset of index exacerbation: Median days to recovery: 11 [Q1, Q3: 6, 22][f] Gradual onset of index exacerbation: Median days to recovery: 13 [Q1, Q3: 7, 29][g]
Farias 2019[69]	Treated recovery time: time elapsed between medication start date and exacerbation end date Exacerbation recovery time: time elapsed between exacerbation start and end date	68 exacerbations	Canada	Outpatient	Initial study visit	Mean days of treated recovery time: 10.4 [SD 10.5] Mean days of exacerbation recovery time: 13.3 [SD 13.3]
Hurst 2009[28]	Time to Recovery: number of days from exacerbation onset to first of 2 consecutive symptom-free days	410 exacerbations	UK, London COPD Cohort	Outpatient	Onset of index exacerbation	Median time to recovery: 5 [Q1, Q3: 3, 8]
Liang 2017[66]	Time to Recovery: self-reported recovery period	890	China	Cohort study	Following last COPD exacerbation	Mean days to recovery among patients with bronchitis: 19 [SD: 16.2] Mean days to recovery among patients without bronchitis: 15.2 [SD 14.7]
Mackay 2014[67]	Time to Recovery: number of days that major lower airway symptoms (dyspnea, sputum volume, sputum purulence) were still being recorded	128 exacerbations	UK, London COPD Cohort	Outpatient	Onset of exacerbation	Median days to recovery: 7 [Q1, Q3: 0, 12]
Minov 2018[36]	Time to Recovery: Resolution of cardinal symptoms or return to baseline severity	54	Macedonia	Outpatient	Onset of index exacerbation	Mean days to recovery: 5.2 [SD 1.1]
Miravitlles 2003[38]	Time to Recovery: number of days required for symptoms to return to baseline	441	Spain	Outpatient clinic	Following initial exacerbation Initiation of antibiotic therapy	Mean days to recovery: 4.6 [SD 3.3]
Miravitlles 2005[57]	Time to Recovery: number of days for symptoms to return to baseline	1147	Spain	Primary care	Onset of index exacerbation	Median: 5 days[g]
Miravitlles 2009[68]	Time to Recovery: physician assessment of antibiotic therapy; patient reports number of days to feeling better	9225	GIANT[h]	Outpatient	Initial clinic visit	Physician assessed: 6.3 [SD: 3.1] Patient report: 7.3 [SD 3.1]
Wilkinson 2004[65]	Time to Recovery: time for 3-day moving average of total daily symptom count to return to baseline	1099 exacerbations	UK, London COPD Cohort	Outpatient	Onset of exacerbation	Median days to recovery: 10.7 [Q1, Q3: 7, 14]

Notes: [a]N represents patients unless otherwise noted; [b]Days unless otherwise specified; [c]GIANT study, worldwide; [d]Late recovery defined as ≥8 days, early recovery defined as ≤4 days; [e]MARC study, USA and Canada; [f]Sudden exacerbations had an onset of 0 days and "gradual" exacerbations had an onset of 4 days with starting point after 5 consecutive days free of symptoms; [g]No measure of spread reported; [h]GIANT study, European.

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; MARC, Medication Adherence Research in COPD Patients; PEF, peak expiratory flow; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; UK, United Kingdom.

Table 5 Summary of the Four Terms Identified to Describe Subsequent AECOPD Events

Relapse	Typically defined as a re-visit to the emergency department or other physician visit for worsening symptoms within 5–30 days of presentation to clinician
Re-exacerbation /recurrence	Subsequent exacerbation typically within 1–6 months from hospital discharge or following X consecutive days free of recorded symptoms
Treatment failure	Definition typically included death and/or was related to in-hospital failure. Often overlapping with relapse and non-recovery terms/definitions. Predominantly measured in hospital settings within 1 month of either initial AECOPD visit or discharge
Non-recovery/time to recovery	(Includes late recovery, non-recovery and ongoing AECOPD.) Non-recovery typically defined using daily diaries as not returning to baseline within 30–90 days from onset of initial AECOPD. Time to recovery often defined based on self-reported symptom recording, and often specified a return to baseline

Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

In the literature, the distinction between the terms recurrence and re-exacerbation was unclear, and so these two terms were grouped in our analysis. Definitions for treatment failure and relapse often overlapped, such as a return to the ED or a hospital readmission. Definitions for non-recovery were generally distinct, with half of the studies using the term "non-recovery" set in the same cohort. Only one study elucidated the importance of the difference between the definitions of relapse and recurrence, where relapse is treatment failure of a first exacerbation and recurrence is a subsequent AECOPD after successful treatment.[28]

Terms used to define subsequent AECOPD-related events seem to be chosen pragmatically rather than based on any existing standards, and may be driven by external considerations (eg, incentives/penalties associated with readmissions for COPD within 30 days such as the Hospital Readmission Reduction Program in the US)[74] rather than event time course or disease phenotypes. These factors may contribute to the observed heterogeneity, making definitions of subsequent AECOPDs dependent on healthcare setting and partly explaining the large variation in estimates of subsequent AECOPD-related events defined using the four terminology and definition clusters. The available evidence suggests that the use of event- or symptom-based approaches may lead to substantially different conclusions regarding occurrence of exacerbations.[75]

In general, the time frames for observing an AECOPD described as a relapse were shorter (up to 30 days) than those for recurrences/re-exacerbations (up to 365 days); time frames for treatment failure and non-recovery were similar (up to approximately 90 days). For all four "subsequent AECOPD" terminology groups, the defined "end" of an initial exacerbation (ie, starting point for observing subsequent events) was variable but frequently included start or end of hospital admission or an ED visit. Re-exacerbation/recurrence was commonly used in the studies with follow-up after hospital admission. The term "treatment failure" was also used frequently in the hospital setting. Non-recovery and relapse study settings were heterogenous.

We observed that the choice of the starting point for measuring subsequent AECOPD can have an important impact on estimates of the proportion of patients experiencing these subsequent events. For example, as a patient cannot experience a re-exacerbation whilst their index exacerbation is ongoing, the proportion of patients experiencing a relapse within 30 days of an index exacerbation will be higher when the 30-day timeframe begins after the exacerbation has ended than when the timeframe begins 5 days after the start of steroid treatment, for example. Exacerbation duration is variable and can be lengthy in some patients and may depend on severity, therefore estimates of subsequent AECOPD will be biased when looking for subsequent events before a patient has recovered or returned to baseline from their initial exacerbation.[22]

Similarly, exacerbation recovery will appear longer when measured from the onset of symptoms than upon hospital admission. Most of the studies using the term non-recovery used onset of exacerbation as a starting point; however, all these studies were set in the London COPD cohort. The other two studies using non-recovery were also in the same cohort (Medication Adherence Research in COPD Patients cohort) and used presentation to the ED as the starting point. The starting point for re-exacerbation /recurrence in the hospital setting was primarily hospital discharge. Of note, one study set in the London COPD cohort used the term re-exacerbation/recurrence with a starting point as five days free of all recorded symptoms,[28] while another study also using re-

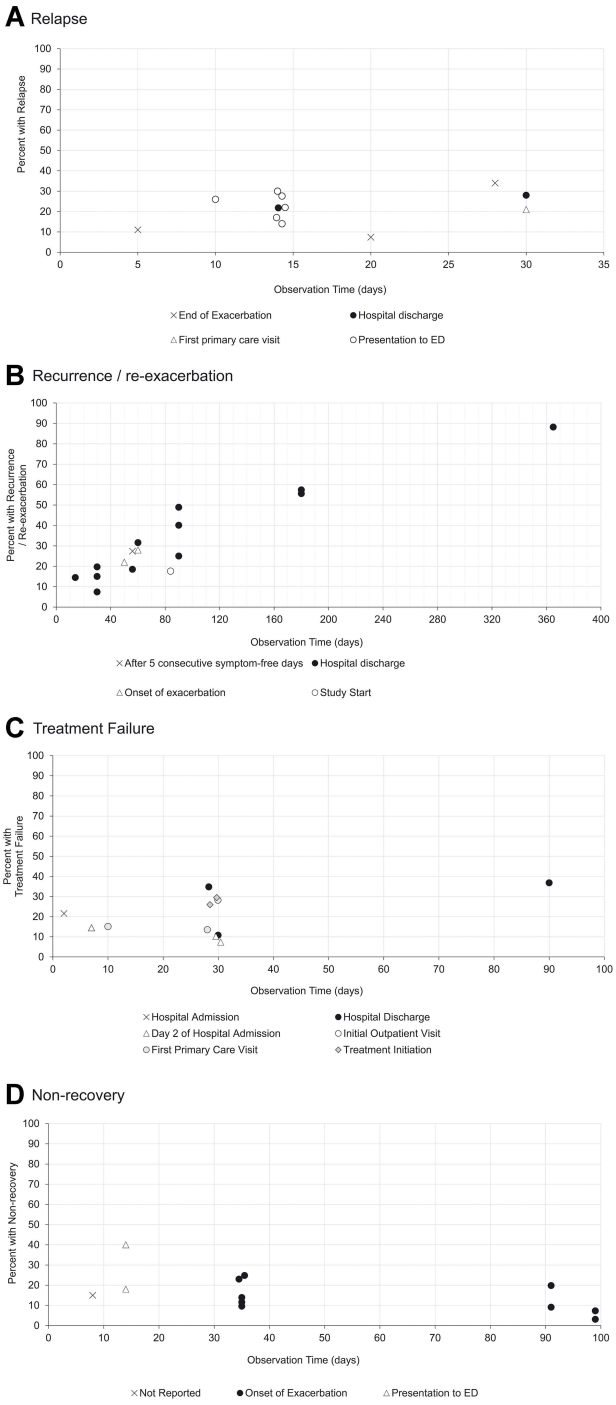

Figure 2 Reported proportions of patients with (**A**) relapse event, (**B**) recurrence/re-exacerbation event, (**C**) treatment/clinical failure, and (**D**) non-recovery, by starting point of observation time frame. (**A**) Includes estimates from 12 observational studies reporting outcomes using a relapse term and definition. Defined as a re-visit to the emergency department or physician for a worsening of symptoms but typically not differentiated from "recurrence" or "re-exacerbation". One study used two definitions for relapse at 14 days and thus has two data points. Domenach (2013) is not plotted because the study did not report a timeframe. (**B**) Includes estimates from 10 observational studies reporting outcomes using a recurrence/re-exacerbation term and definition. Mostly defined as a "re-exacerbation" (n = 3), a prescription course of corticosteroids or antibiotics (n = 3), or as a composite outcome (n = 3) including death or AECOPD treatment and/or remission. Some studies (n = 4) required recovery of initial AECOPD prior to subsequent AECOPD. Two studies have data points at several time horizons (30, 90, 180, and 365 days from Wang et al [2012] and 30, 60, 90, and 180 days from Johannesdottir et al [2013]). Bartziokas et al (2014) reported proportion at 3 months and 6 months in "low uric acid" and "high uric acid" groups, but not overall, and therefore these data points are not presented in the figure. (**C**) Includes estimates from 12 observational studies reporting outcomes using a treatment failure term and definition with some definitions similar to relapse and non-recovery. Often included death (n = 7) and/or was related to in-hospital treatment failure (n = 6). (**D**) Includes estimates from seven observational studies reporting outcomes using a non-recovery term and definition. Some studies (n = 2) reported estimates at multiple time points and using different methods of measurement (eg, non-recovery ascertained daily symptom score reports or spirometry). Most were from the London COPD cohort. Two studies have multiple data points due to different measurement methods (symptom report and peak expiratory flow, Donaldson [2015] and Seemungal [2000]) over several time horizons (Seemungal [2000] at 35 days and 91 days).

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ED, emergency department.

exacerbation/recurrence and set in the London CODP cohort used onset of exacerbation, similar to the London COPD studies using non-recovery.[48]

In addition to heterogeneity in the terms, timeframes and starting points for subsequent AECOPD events, we also observed heterogeneity in the study setting. Studies using the term relapse were often set in the ED, whilst most studies conducted in the hospital setting used the term treatment failure. Overall, this heterogeneity has driven variation in the proportion of patients experiencing subsequent events. For example, the proportion of patients with exacerbation relapse ranged from 7.4% at 20 days[36] to 34% at one month,[38] with variability (due to differing starting point for follow-up) appearing to have a greater impact on the relapse estimate then the length of follow-up (intuitively, we would expect to see greater proportions of patients experiencing relapse when the length of follow-up for relapse is increased).

There are several potential explanations for our finding that no standard definitions exist. First, exacerbations are heterogenous in terms of symptoms, etiology (bacterial vs viral, specific pathogens vs common pollutants), and time course.[71,76,77] Second, there is variation in data sources, primary versus secondary data collection, and availability of specific data to define a re-exacerbation (eg, prescriptions for oral corticosteroids, self-reported symptoms). Finally, specific research questions often drive the type of data collected, and variability by definitions used in different guidelines and countries can contribute to heterogeneity.

Change begins with a recognition of the need for change, and this paper demonstrates that need by highlighting the large amount of heterogeneity between studies. Our finding of common core domains for each definition may be useful for developing an agreed consensus definition for classifying recurring exacerbations, treatment failure, and recovery from AECOPD. As a first step, we believe clear exacerbation definitions are required[19,24] and that these should be determined by a consensus of experts (for example through a Delphi study) and cascaded via global guideline groups. Then, specific definitions are needed to enable differentiation between distinct AECOPD events. Without standard definitions, our ability to advance the understanding and natural history of AECOPD is impaired.

Strengths of this study include the systematic approach, and the comprehensive, international scope of the literature review. Additionally, studies were not excluded on the basis of quality which allowed us to describe the breadth of definitions currently in the literature. Nonetheless, there are limitations of our research which should be considered when interpreting our findings. First, studies where subsequent AECOPDs were defined as hospital readmission alone were excluded. Second, the included studies were not always explicit in definitions, particularly regarding the index date for recurrent AECOPD events which makes interpretation of the proportion of patients experiencing a subsequent AECOPD difficult. Third, subsequent AECOPD definitions may also differ to randomized clinical trials. This review focused on observational studies; however, a review of the terminology used in randomized clinical trials was presented previously and may better inform how terminology can be standardized to allow for better comparison of treatments.[78]

Conclusion

In conclusion, our systematic review demonstrates that the concept of subsequent AECOPD is ill-defined in the observational study literature, thus emphasizing the need for rigorous attempts to reach a consensus on a more precise and objective definition for subsequent AECOPDs. Use of standardized terminology and definitions may aid comparability and synthesis of studies, thus improving the understanding of the natural history of AECOPD.

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Author Contributions

VSB and HM contributed to the conception and design of the study, data acquisition, data analysis and interpretation. BMD contributed to the data acquisition, analysis and interpretation. WHM, BMD and WF contributed to the data analysis and interpretation. All authors made critical revisions to the draft versions of manuscript and approved the final manuscript, reviewed and agreed on all versions of the article before submission, during revisions, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors agreed on the journal to which the article would be

submitted and agree to take responsibility and be accountable for the contents of the article.

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WAF and VSB are employees of, and hold shares in, GlaxoSmithKline plc. WHM and HM were employees of GlaxoSmithKline plc. at the time the study was conducted; WHM and HM are currently employees of AstraZeneca. BMD is a PhD candidate at University of North Carolina at Chapel Hill and works for GlaxoSmithKline plc. as a Research Assistant. The authors report no other conflicts of interest in this work.

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