MANAGEMENT OF COPD EXACERBATIONS

Online supplement

TABLE OF CONTENTS

DIAGNOSIS AND EVALUATION

What is the optimal approach to diagnose a COPD exacerbation?

Diagnosis of an exacerbation is generally based upon an acute worsening of the patient's usual pattern of respiratory symptoms: increased dyspnea, cough, sputum, and/or sputum purulence. There is no validated biomarker of a COPD exacerbation. Respiratory tract infection with bacteria or viruses seems to be the most common cause. Some exacerbations are mild and self-limiting and may not be reported to healthcare professionals (1,2), instead being managed by patients at home on their own. Other exacerbations are moderate and severe and require ambulatory treatment and hospitalisation, respectively.

The diagnostic evaluation should include an assessment of the severity of the exacerbation. A number of factors should be considered when evaluating the severity of an exacerbation, including the severity of symptoms (particularly dyspnea), the presence of certain clinical signs (cyanosis, increased respiratory effort, and altered mentation), reductions in physical activity tolerance, and the severity of

airway obstruction. Not all will be present, but the co-occurrence of several of these symptoms and signs should alert the clinician of a severe exacerbation. The decision about whether or not to refer the patient to a hospital requires that the severity of the exacerbation be considered in the context of the patient's age and preferences regarding intensive therapy, social support and co-morbidities. In some circumstances, other investigations may also help in the decision-making regarding hospitalization or in ensuring that appropriate therapy is provided, such as an assessment of hypoxemia, hypercapnia, electrocardiogram, and spirometry with flow-volume loops. Further research is needed to define the optimal approach to diagnose a COPD exacerbation, including the development and validation of biomarkers.

What are the conditions to consider in the differential diagnosis?

Several conditions may result in symptoms and signs similar to those of a COPD exacerbation or co-occur along with a COPD exacerbation and, therefore, should be investigated in patients suspected of having a COPD exacerbation (Table S1). These conditions include the following: pneumonia, pulmonary embolism, pneumothorax, pleural effusion, congestive heart failure (i.e., left ventricular failure/pulmonary edema), ischemic heart disease, cardiac dysrhythmia, lung cancer, tuberculosis, upper airway obstruction, and aspiration.

What tests are required to assess the severity of an exacerbation?

Clinical signs, including limited respiratory effort, cyanosis, and diminished level of consciousness indicate a severe exacerbation. Diagnostic testing may be helpful in patients having a COPD exacerbation (Table S2). Pulse oximetry may assist in the decision about whether or not to perform arterial blood gas measurements (generally performed if the resting SpO_2 is <92% and/or the SpO_2 decreases >5% during mild exertion) and is also useful for adjusting and monitoring supplemental oxygen therapy. Arterial or venous blood gases measurement is needed to identify hypercapnia (generally defined as PaCO2 greater than 45 mmHg), which may occur in patients with acute or acute-on-chronic respiratory failure. This can help determine the adequacy of ventilation in spontaneously breathing patients, as well in patients treated with mechanical ventilation. Arterial blood gases measurement has the added advantage of assessing oxygenation.

Spirometry is not a routine part of the evaluation or management of a COPD exacerbation because it can be difficult to perform due to patient's symptoms, although one study found that adequate quality spirometry can be obtained in the majority of hospitalized, non-intensive care patients (3). However, if a patient has never had spirometry confirming airflow obstruction and is not responding to treatment recommendations in this guideline, spirometry with flow volume loops in the acute setting can be useful in excluding alternative diagnoses, including upper airway obstruction (4-6).

In exacerbations treated in hospital, a chest X-ray can help to exclude other medical conditions. Exacerbations associated with airway bacterial infection usually present with increased sputum purulence (7). If a bacterial exacerbation does not respond to the initial antibiotic therapy, then a sputum culture with antibiotic sensitivity testing may help guide further therapy. Endotracheal aspiration may also be helpful in hospitalized patients who require invasive mechanical ventilation. Routine culture of sputum for all patients is considered to be of limited benefit, although it is occasionally performed for surveillance of antimicrobial resistance.

Blood tests are routine in hospitalized patients or patients with severe disease. Whole blood count may reveal increased total white blood cells count, polycythemia, or anemia. Biochemical tests (electrolytes, glucose, creatinine, urea, D-dimer) may reveal abnormalities associated with COPD exacerbation and/or co-morbidities that could contribute to a more severe COPD exacerbation. An electrocardiogram (ECG) or biomarkers of myocardial injury (e.g., serum troponin levels, creatine kinase-MB), chest computerized tomography with intravenous contrast for pulmonary embolism, echocardiography, and/or thoracic ultrasound may identify conditions that could contribute to a more severe COPD exacerbation or mimic a COPD exacerbation. Further research is needed to define the optimal approach for assessing the severity of COPD exacerbations, as well as tests needed to identify co-occurring conditions in patients with COPD exacerbations.

How should a patient be followed during recovery from a COPD exacerbation?

It is important to monitor the response of a COPD exacerbation to treatment, but the optimal approach for individual patients is not well understood. Regular assessment of clinical symptoms and signs, as well as observation of the patient's functional capacity can help identify the need for treatment intensification for COPD, complications of therapy (e.g., diarrhea), or the presence of additional co-occurring conditions. Pulse oximetry should be used to monitor the recovery of patients with hypoxemic

respiratory failure, whereas arterial blood gas measurements should be used to monitor the recovery of patients with respiratory failure who are hypercapnic and/or acidotic until they are stable. In their clinical practices, most of the guideline panel members follow the oxygenation of patients who are hypoxemic during an exacerbation for the initial three months following discharge to determine whether or not there are indications for initiating, continuing, or discontinuing long-term oxygen therapy at home. Daily monitoring of pulmonary function tests should not be performed during recovery from a COPD exacerbation. Recent data suggest that patients hospitalized for COPD exacerbation are at less risk for rehospitalisation if an outpatient evaluation occurs early in the post hospitalization period (8). Patients with exacerbations treated in the community are likely to require similar follow up to ensure improvement. Further research is needed to define the optimal approach for follow-up in patients recovering from a COPD exacerbation.

References

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Tables

Table S1: Differential Diagnosis of a COPD exacerbation

Infectious
Pneumonia
Tuberculosis
Cardiac
Congestive heart failure
Ischemic heart disease
Cardiac dysrhythmia (e.g., atrial fibrillation with rapid ventricular response, supraventricular tachyarrythmia, bradycardia)
Pleural
Pneumothorax
Pleural effusion
Other
Upper airway obstruction
Pulmonary embolism
Lung cancer

Aspiration

Table S2: Diagnostic tests used to evaluate patients with a possible COPD exacerbation

Diagnostic test	Rationale
Pulse oximetry	Assists in the decision of whether or not to perform arterial blood gases and is useful for adjusting and monitoring supplemental oxygen therapy.
Arterial blood gases	Identifies need for ventilatory support or changes in the level of support using non-invasive or invasive mechanical ventilation; arterial blood gases are also preferred to assess oxygenation over pulse oximetry in cases of suspected methemoglobinemia or carboxyhemoglobinemia.
Chest radiograph	Used to exclude other medical conditions or identify co-existing conditions (e.g., heart failure).
Sputum culture	Useful to identify antibiotic-resistant pathogens in patients whose exacerbation is due to a bacterial infection and has not improved with initial antibiotic therapy.
Blood tests	A whole blood count may identify leukocytosis, polycythemia, or anemia. Biochemical tests may reveal abnormalities associated with COPD or co-morbidities.
Electrocardiogram	May identify coexisting cardiac disease (dysrhythmias, ischemia)
Biomarkers of myocardial injury	Use to examine the presence of myocardial injury that can exist alone or co-occur during COPD exacerbations
Spirometry with flow volume loops	Useful to confirm obstructive lung disease in patients who have never had spirometry or to evaluate possibility of upper airway obstruction in patients with an atypical presentation

LITERATURE SEARCH STRATEGIES

Embase

1.50
#1.43 AND **#1.49**
#1.49
#1.44 OR **#1.45** OR **#1.46** OR **#1.47** OR **#1.48**
#1.48
exacerb*:ab,ti AND [2003-2012]/py
#1.47
exacerbat*:ab,ti AND [2003-2012]/py
#1.46
(**acute** NEXT/3 **exacerbation***):ab,ti AND [2003-2012]/py
#1.45
aggravation:ab,ti AND [2003-2012]/py
#1.44
exacerbation*:ab,ti AND [2003-2012]/py
#1.43
#1.42 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [english]/lim AND [2003-2012]/py
#1.42
#1.41 AND [english]/lim AND [2003-2012]/py
#1.41

#1.39 NOT **#1.40**
#1.40
'child'/exp OR **'newborn'**/exp NOT **'adult'**/exp
#1.39
#1.23 NOT **#1.38**
#1.38
#1.24 OR **#1.25** OR **#1.26** OR **#1.27** OR **#1.28** OR **#1.29** OR **#1.30** OR **#1.31** OR **#1.32** OR **#1.33** OR **#1.34** OR **#1.35** OR **#1.36** OR **#1.37**
#1.37
'rodent'/exp
#1.36
'animal model'/exp
#1.35
'animal experiment'/exp
#1.34
'experimental animal'/exp
#1.33
'animals, laboratory'/exp
#1.32
'animal studies'/exp
#1.31
'nonhuman'/exp
#1.30
'animal'/exp NOT (**'animal'**/exp AND **'human'**/exp)
#1.29
'case study'/exp
#1.28
'case report'/exp
#1.27
note:it
#1.26
editorial:it
#1.25
'letter'/exp
#1.24
letter:it
#1.23
#1.10 NOT **#1.22**
#1.22
#1.11 OR **#1.12** OR **#1.13** OR **#1.14** OR **#1.15** OR **#1.16** OR **#1.17** OR **#1.18** OR **#1.19** OR **#1.20** OR **#1.21**
#1.21
asthma:ti
#1.20
'asthma'/exp
#1.19
(**interstitial** NEXT/2 (**lung** OR **pulmonary** OR **airway*** OR **airlfow***)):ti
#1.18
interstitial:ti
#1.17
bronchiolitis:ti OR **bronchiectasis**:ti
#1.16
'sleep apnea':ti
#1.15
'acute bronchitis':ti
#1.14
cancer:ti OR **neoplas***:ti
#1.13
'lung dysplasia'/exp
#1.12

'sleep apnea syndrome'/exp
#1.11
'bronchial neoplasms'/exp OR **'bronchiectasis'**/exp OR **'bronchiolitis'**/exp OR **'cystic fibrosis'**/exp OR **'lung diseases, interstitial'**/exp OR **'lung neoplasms'**/exp
#1.10
#1.1 OR **#1.2** OR **#1.3** OR **#1.4** OR **#1.5** OR **#1.6** OR **#1.7** OR **#1.8** OR **#1.9**
#1.9
'chronic bronchitis':ab,ti
#1.8
emphysema:ab,ti
#1.7
'lung emphysema'/exp
#1.6
(**chronic** NEXT/5 **obstruct***):ti OR (**chronic** NEXT/5 **limit***):ti
#1.5
'chronic bronchitis'/exp
#1.4
'bronchitis'/exp
#1.3
coad:ab,ti
#1.2
copd:ab,ti
#1.1
'chronic obstructive lung disease'/exp

Medline (via Ovid)

1. exp Pulmonary Disease, Chronic Obstructive/
2. copd.ti,ab.
3. coad.ti,ab.
4. Bronchitis/
5. Chronic bronchitis/
6. (chronic adj5 (obstruct$ or limit#$)).ti.
7. (obstruct$ adj3 (airflow$ or airway$ or respirat$ or lung or pulmonary) adj2 (disease$ or disorder$)).ti,ab.
8. Pulmonary emphysema/
9. emphysema.ti,ab.
10. "chronic bronchitis".ti,ab.
11. or/1-10
12. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/
13. exp Sleep Apnea Syndromes/
14. Bronchopulmonary Dysplasia/
15. (cancer or neoplas$).ti.
16. "acute bronchitis".ti.
17. sleep apnea.ti.
18. (bronchiolitis or bronchiectasis).ti.
19. interstitial.ti.
20. (interstitial adj2 (lung or pulmonary or airway$ or airflow$)).ti.
21. exp Asthma/
22. asthma.ti.
23. or/12-22
24. 11 not 23
25. letter/
26. editorial/
27. exp historical article/
28. Anecdotes as Topic/
29. comment/
30. case report/
31. animal/ not (animal/ and human/)
32. Animals, Laboratory/
33. exp animal experiment/

34. exp animal model/
35. exp Rodentia/
36. or/25-35
37. 24 not 36
38. limit 37 to english language
39. (exp child/ or exp infant/) not exp adult/
40. 38 not 39
41. "review"/ or review.pt. or review.ti.
42. (systematic or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab.
43. 41 and 42
44. meta-analysis.pt.
45. Meta-Analysis/
46. exp Meta-Analysis as Topic/
47. (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).mp.
48. ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh.
49. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
50. or/43-49
51. randomized controlled trial.pt.
52. controlled clinical trial.pt.
53. double-blind method/ or random allocation/ or single-blind method/
54. exp Clinical Trial/
55. exp Clinical Trials as Topic/
56. clinical trial.pt.
57. random$.ti,ab.
58. ((clin$ or control$) adj5 trial$).ti,ab.
59. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
60. Placebos/ or placebo$.ti,ab.
61. (volunteer$ or "control group" or controls or prospectiv$).ti,ab.
62. Cross-Over Studies/
63. ((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.
64. or/51-63
65. 50 or 64
66. 40 and 65
67. aggravation.ti,ab.
68. attack.ti,ab.
69. (acute adj3 exacerbation$).ti,ab.
70. exacerbation$.ti,ab.
71. exacerbat$.ti,ab.
72. or/67-71
73. 66 and 72
74. limit 73 to yr="2003-current"

RESEARCH PROTOCOLS (INCLUDING STUDY SELECTION CRITERIA)

Research Protocol, Question 1	
Question	Should **oral corticosteroids** be used to treat **ambulatory** patients who are having a COPD exacerbation?
Objective	To compare the use of oral corticosteroids to placebo in patients with COPD exacerbations treated in the community setting as outpatients.
Study selection criteria	Randomized trials (or systematic reviews of randomized trials) comparing oral corticosteroids to placebo in adults with acute exacerbation of COPD.
Outcomes	• Treatment failure (critical) • Hospital admission (critical)

	• Mortality (critical) • Time to next exacerbation (critical) • Quality of life (important) • Adverse events (important) • Forced expiratory volume in one second (not important)
Search strategy	Shown above

Research Protocol, Question 2	
Question	Should intravenous or oral corticosteroids be used to treat patients who are hospitalized due to a COPD exacerbation?
Objective	To compare the use of intravenous and oral corticosteroids in patients hospitalized for a COPD exacerbation
Study selection criteria	Randomized trials (or systematic reviews of randomized trials) comparing IV to oral corticosteroids in adults hospitalized with acute exacerbation of COPD.
Outcomes	• Treatment failure (critical) • Mortality (critical) • Hospital admissions (critical) • Length of hospital stay (critical) • Time to next exacerbation (critical) • Adverse events (important)
Search strategy	Shown above

Research Protocol, Question 3	
Question	Should antibiotics be administered to ambulatory patients who are having a mild to moderate COPD exacerbation?
Objective	To compare the use of antibiotics versus placebo in ambulatory patients with COPD exacerbations
Study selection criteria	Randomized trials (or systematic reviews of randomized trials) comparing antibiotics versus placebo in ambulatory patients with COPD exacerbations
Outcomes	• Treatment failure (critical) • Mortality (critical) • Hospital admissions (critical) • Length of hospital stay (critical) • Time to next exacerbation (critical) • Adverse events (critical) • Peak expiratory flow rate (not important)
Search strategy	Shown above

Research Protocol, Question 4

Question	Should non-invasive mechanical ventilation be used in patients who are hospitalized with a COPD exacerbation (especially within the initial 24 hours after presentation)?
Objective	To compare NIV to any other treatment administered to COPD patients within 24h of presentation
Study selection criteria	Randomized trials (or systematic reviews of randomized trials) comparing NIV with any other intervention administered within 24h of presentation in hospitalized COPD patients
Outcomes	• Mortality (critical) • Need for intubation (critical) • Length of hospital stay (critical) • Length of ICU stay (critical) • Nosocomial pneumonia (critical) • Complications of treatement (important) • Changes in blood gases (important)
Search strategy	Shown above

Research Protocol, Question 5	
Question	Should a "hospital at home" program be implemented in patients whose COPD exacerbation is sufficiently severe that they would otherwise require hospitalization?
Objective	To compare hospital at home management to usual care in patients with severe COPD exacerbations that would require hospitalization
Study selection criteria	Randomized trials (or systematic reviews of randomized trials) comparing hospital at home management of COPD exacerbations to usual care
Outcomes	• Hospital readmission (critical) • Mortality (critical) • Time to first readmission (critical) • Hospital acquired infections (important) • Quality of life (important) • Forced expiratory volume in one second (not important)
Search strategy	Shown above

Research Protocol, Question 6	
Question	Should pulmonary rehabilitation be implemented in patients hospitalized with a COPD exacerbation?
Objective	To compare the implementation of "early" rehabilitation to usual care in hospitalized patients with COPD exacerbations
Study selection criteria	Randomized trials (or systematic reviews of randomized trials) comparing early rehabilitation (max 4 weeks after exacerbation) to usual care in hospitalized patients with COPD exacerbations
Outcomes	• Hospital readmission (critical) • Mortality (critical)

	• Quality of life (critical) • Exercise tolerance (important)
Search strategy	Shown above