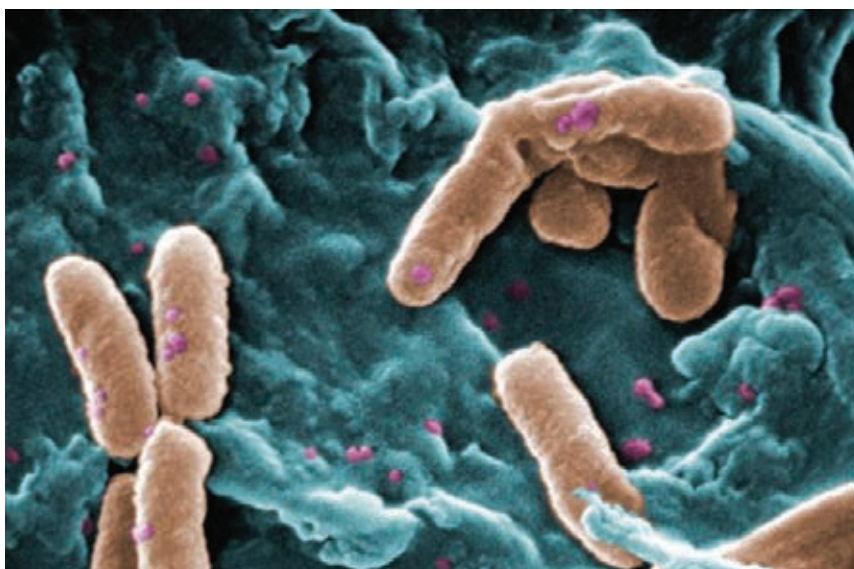


# The pathogenesis of acute infection in COPD



A. Anzueto

(111E) Pulmonary/critical care  
7400 Merton Minter Boulevard  
San Antonio  
TX 78229  
USA  
E-mail: [anzueto@uthscsa.edu](mailto:anzueto@uthscsa.edu)

## Provenance

Adapted from an ERS Postgraduate Course

## Competing interests

The author has acted as a consultant or speaker for companies that make antibiotics, bronchodilators and pulmonary-related products. The author has received research grants from GlaxoSmithKline, Intermune and Bayer Pharma.

## Educational aims

- › To give an overview of the types of infectious agents involved in causing acute exacerbations of chronic obstructive pulmonary disease (COPD).
- › To outline the mechanisms through which infectious agents drive exacerbations.
- › To introduce the concept that mixed infections may increase the severity of exacerbations.

## Summary

Infectious agents are implicated in a large majority of acute COPD exacerbations. The compromised defences of the patient's tracheobronchial system make it vulnerable to infection, with the consequent inflammatory and immune responses.

A number of virulence factors have been associated with bacterial pathogens' propensity to cause exacerbations, and the genetic basis for these has begun to be examined. In addition, the acquisition of new strains of some bacteria has been associated with exacerbations. Viral nucleic acids are detected in about half of exacerbations, and several viruses are implicated, in particular rhinovirus. The manner in which these and other pathogens, individually and collectively, interact with the host merits further scrutiny if the prevention and treatment of acute COPD exacerbations are to be improved.

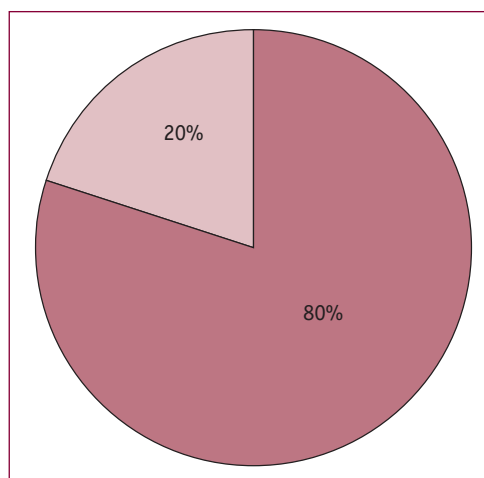
HERMES syllabus link: modules B.1.4, B.3

Acute exacerbations of COPD are a significant cause of morbidity and mortality and are associated with frequent visits to physicians and hospitalisations. Thus, this condition results in significant economic burden to healthcare systems. The causes of acute COPD exacerbations may be multi-factorial. Viral infections and/or levels of air pollution may exacerbate the existing inflammation in the airways, which in turn, may predispose patients to secondary bacterial infections. Infectious agents, including bacteria, viruses and atypical pathogens, are currently implicated in up to 80% of acute exacerbations of COPD (figure 1) [1].

A considerable body of empirical evidence now supports the concept that exacerbations are acute inflammatory events superimposed on the chronic inflammation characteristic of COPD [2-5]. Several inflammatory cells and molecules measured in exhaled breath, induced or expectorated sputum, bronchoalveolar lavage (BAL) or bronchial biopsy have been found to be elevated during acute exacerbations [6]. Furthermore, increased levels of plasma fibrinogen, interleukin (IL)-6, C-reactive protein and procalcitonin have been noted during exacerbations, demonstrating increased systemic inflammation [7].

A normal tracheobronchial tree has innate defence mechanisms to maintain sterility. These are compromised in the airway of COPD patients, allowing the microbial pathogens to become established and proliferate in the lower airway. Inflammatory and adaptive immune responses are recruited to deal with these proliferating microbial pathogens [8-11]. Increased levels of inflammatory cells and cytokines induce airway secretions, bronchospasm and mucosal oedema, which in turn lead to worsening ventilation/perfusion mismatch and hyperinflation, resulting in acute changes in the patient's symptoms.

**Figure 1**  
Aetiology of acute exacerbations of COPD. ■ : noninfections, environmental factors and noncompliance with medications; ■ : infections, bacterial pathogens 40-50%, viral infection 30-40% and atypical bacteria 5-10%. Data from [1].

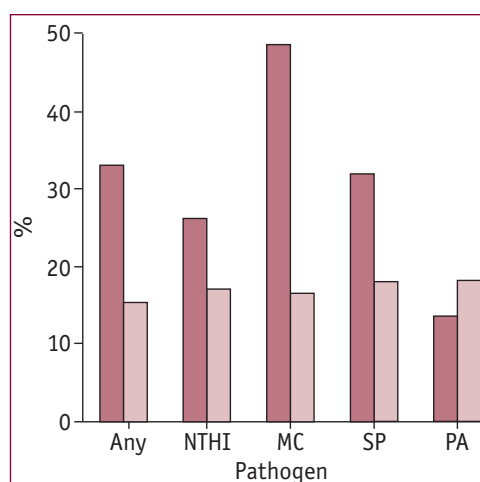


**Figure 2**  
COPD study clinic - new strain isolation and exacerbation. NTHI: nontypeable H. influenzae; MC: M. catarrhails; SP: S. pneumoniae; PA: P. aeruginosa. ■ : new strain positive; ■ : new strain negative. data from [13].

## Bacteria

The results of recent studies demonstrate that the acquisition of new bacterial strains, mainly nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*, appears to be the predominant initiating event for an acute exacerbation of COPD (figure 2) [12, 13]. The acquisition of new strains of *Pseudomonas aeruginosa*, however, is not related to acute exacerbations [13]. The balance between host defence and pathogen virulence determines the level of proliferation of the pathogen (the bacterial load), which in turn determines the increase in airway inflammation. Large increases in airway inflammation result in greater pathophysiological changes, which lead to symptoms intense enough for the patient to seek healthcare, and often to be diagnosed as experiencing an exacerbation. Conversely, if there is a limited increase in airway inflammation, symptoms may not increase to such an intensity that an exacerbation is diagnosed. Furthermore, over time, the development of an adaptive immune response may limit the proliferation of the pathogen, or regulatory mechanisms may dampen the inflammation, though the bacterial strain may persist. In these situations, the bacterial infection would be regarded as colonisation. To add to the complexity, patient perception, access to care and physician interpretation of symptoms are additional determinants of the diagnosis of exacerbations.

Putative pathogen virulence factors for respiratory bacterial pathogens include adhesion to and invasion of airway epithelial cells, inactivation of host defence mechanisms and elicitation of inflammatory mediators from airway cells. Furthermore, exacerbation strains adhered in significantly higher numbers to and elicited more IL-8 from primary airway human airway epithelial cells



in culture when compared with colonising strains (figure 3) [14]. Several investigators have recently published studies examining whether genetic differences underlie the pathogenic potential of *H. influenzae* strains isolated from the sputum of patients with COPD [15]. A specific combination of genes was found to be related to exacerbation, and inactivation of host defences appears to be an important determinant of disease expression among bacterial strains. These observations support pathogen virulence as an important determinant of clinical manifestations of new bacterial strain acquisition in COPD.

Exacerbations are inflammatory events; however, this inflammatory process is not uniform and is related to the aetiology of the exacerbation. Exacerbations associated with bacterial pathogens exhibit significantly more neutrophilic inflammation than nonbacterial episodes [16, 17]. Resolution of symptoms of exacerbations associated with purulent sputum is associated with a consistent decrease in neutrophilic airway inflammation.

*P. aeruginosa* has been isolated from sputum and bronchoscopic samples in COPD exacerbations, usually with underlying severe airflow obstruction. However, for *P. aeruginosa*, an association between exacerbations and new strain isolation was not identified in COPD or in cystic fibrosis. This suggests that alternative mechanisms underlie exacerbations caused by this pathogen, such as biofilm formation, increased bacterial load or reinfection because of a markedly impaired immune response in these sicker patients. Other Gram-negative Enterobacteriaceae and *Staphylococcus aureus* are often isolated from sputum during exacerbations and from bronchoscopy samples obtained during exacerbations of severe COPD.

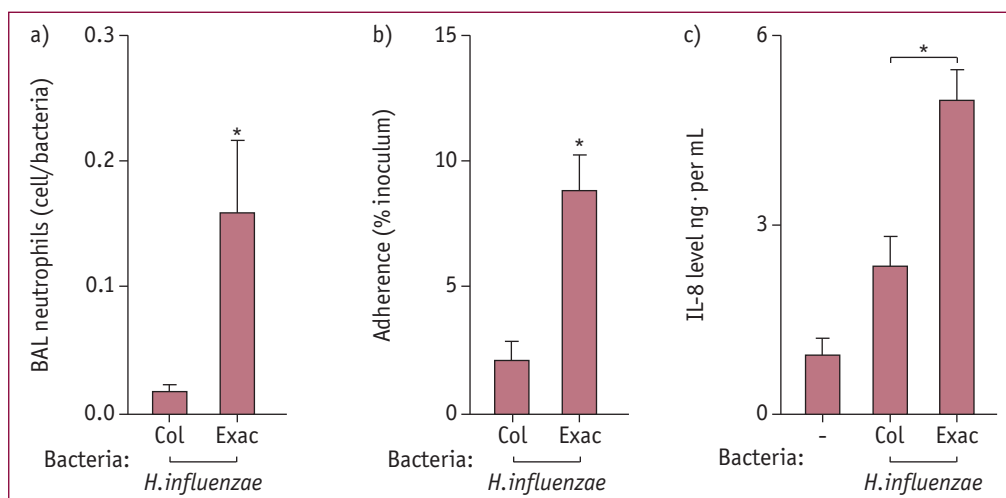
## Viruses

Previous investigations of the viral causation of exacerbations of COPD relied on serological studies and on viral cultures of upper airway samples. Now, investigators are using PCR-based detection of viral nucleic acids in sputum samples and are able to detect viral nucleic acids in 48–56% of exacerbations and 6–19% of controls. PAPI *et al.* [4] found that sputum eosinophilia was characteristic of exacerbations of viral aetiology. With widespread use of the influenza vaccine, rhinovirus has become the predominant virus implicated in exacerbations [18, 19]. Respiratory syncytial virus is also now recognised as capable of causing significant illness in elderly adults with chronic lung and heart illness [20]. Other viruses associated with exacerbations include influenza, parainfluenza, adenovirus, coronavirus and human metapneumovirus.

## Atypical pathogens and co-infection

The importance of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in acute COPD exacerbations is not well defined [21–24]. The major limitation is related to the diagnostic methods used in studies to define infection with these pathogens. These diagnostic methods include culture of respiratory secretions, PCR detection of microbial DNA and serology.

An antecedent viral infection is not essential for the development of bacterial acute exacerbations. Exacerbations may be attributed to virus alone, to both viral and bacterial infection or to bacterial infection alone [25]. Co-infection by

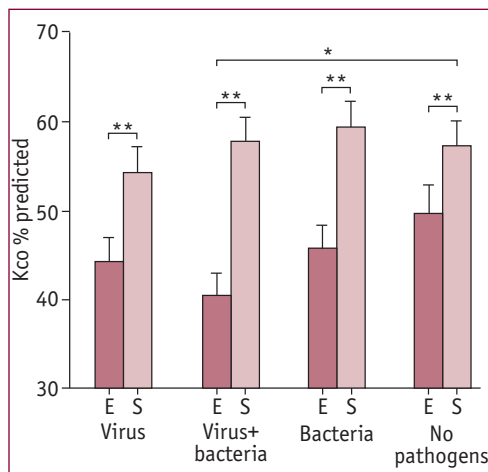


**Figure 3**

Nontypeable *H. influenzae* from patients with acute COPD exacerbations (Exac) elicit greater inflammation and epithelial cell adhesion than colonising (Col) strains. Reproduced from [14], with permission from the publisher.

**Figure 4**

Dual infection is more severe. Kco: diffusion capacity; E: severe exacerbation; S: stable convalescence. \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ .



virus and bacteria does seem to increase the severity of exacerbations, with greater decrement of lung function, higher bacterial loads and more systemic inflammation (figure 4) [3, 4]. Co-infection with *C. pneumoniae* and bacterial infection has also been described, however,

without an impact on the clinical manifestations of exacerbation [22].

## Conclusions

Though substantial progress has been made in the understanding of infectious exacerbations in COPD, much still needs to be learned. The complexity of the host-pathogen interaction that determines the onset and cause of exacerbations needs further exploration, including examination of host cellular and molecular mechanisms, the determinants of pathogen virulence and those pathogens' interaction with airway epithelial cells and macrophages. The interactions of the various causes of exacerbations need to be better understood, to facilitate the development of prevention strategies based on these interactions. Novel methods of treatment and prevention would undoubtedly emerge from such insights into the mechanisms and pathophysiology of exacerbations.

## References

- Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 117: Suppl. 2, 380s–385s.
- Sethi S. New developments in the pathogenesis of acute exacerbations of chronic obstructive pulmonary disease. *Curr Opin Infect Dis* 2004; 17: 113–119.
- Wilkinson T, Hurst J, Perera W, Wilks M, Donaldson G, Wedzicha J. Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of chronic obstructive pulmonary disease. *Chest* 2006; 129: 317–324.
- Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
- Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJB, Murphy TF. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 118: 1557–1565.
- Gompertz S, O'Brien C, Bayley DL, Hill SL, Stockley RA. Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. *Eur Respir J* 2001; 17: 1112–1119.
- Zhu J, Qiu YS, Majumdar S, et al. Exacerbations of bronchitis: bronchial eosinophilia and gene expression for interleukin-4, interleukin-5, and eosinophil chemoattractants. *Am J Respir Crit Care Med* 2001; 164: 109–116.
- Balbi B, Bason C, Balleari E, et al. Increased bronchoalveolar granulocytes and granulocyte-macrophage colony-stimulating factor during exacerbations of chronic bronchitis. *Eur Respir J* 1997; 10: 846–850.
- Saetta M, Di Stefano A, Maestrelli P, et al. Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med* 1994; 150: 1646–1652.
- Hurst JR, Perera WR, Wilkinson TM, Donaldson GC, Wedzicha JA. Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 71–78.
- Crooks SW, Bayley DL, Hill SL, Stockley RA. Bronchial inflammation in acute bacterial exacerbations of chronic bronchitis: the role of leukotriene B4. *Eur Respir J* 2000; 15: 274–280.
- Veeramachaneni SB, Sethi S. Pathogenesis of bacterial exacerbations of COPD. *COPD* 2006; 3: 109–115.
- Sethi S, Evans N, Grant BJB, Murphy TF. Acquisition of a new bacterial strain and occurrence of exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347: 465–471.
- Chin CL, Manzel LJ, Lehman EE, et al. *Haemophilus influenzae* from patients with chronic obstructive pulmonary disease exacerbation induce more inflammation than colonizers. *Am J Respir Crit Care Med* 2005; 172: 85–91.
- Fernaays MM, Lesse AJ, Sethi S, Cai X, Murphy TF. Differential genome contents of nontypeable *Haemophilus influenzae* strains from adults with chronic obstructive pulmonary disease. *Infect Immun* 2006; 74: 3366–3374.
- Murphy TF, Brauer AL, Grant BJ, Sethi S. *Moraxella catarrhalis* in chronic obstructive pulmonary disease: burden of disease and immune response. *Am J Respir Crit Care Med* 2005; 172: 195–199.
- Sethi S, Wrona C, Grant B, Murphy T. Strain specific immune response to *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 448–453.
- Seemungal TA, Harper-Owen R, Bhowmik A, Jeffries DJ, Wedzicha JA. Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 2000; 16: 677–683.
- Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
- Falsey A, Hennessey P, Formica M, Cox C, Walsh E. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005; 352: 1749–1759.
- Blasi F, Damato S, Cosentini R, et al. *Chlamydia pneumoniae* and chronic bronchitis: association with severity and bacterial clearance following treatment. *Thorax* 2002; 57: 672–676.
- Mogulkoc N, Karakurt S, Isalska B, et al. Acute purulent exacerbation of chronic obstructive pulmonary disease and *Chlamydia pneumoniae* infection. *Am J Respir Crit Care Med* 1999; 160:349–353.
- Miyashita N, Niki Y, Nakajima M, Kawane H, Matsushima T. *Chlamydia pneumoniae* infections in patients with diffuse panbronchiolitis and COPD. *Chest* 1998; 114: 969–971.
- Karnak D, Beng-sun S, Beder S, Kayacan O. *Chlamydia pneumoniae* infection and acute exacerbation of chronic obstructive pulmonary disease (COPD). *Respir Med* 2001; 95: 811–816.
- Sethi S. Co-infection in exacerbations of COPD: a new frontier. *Chest* 2006; 129: 223–224.

**Educational questions**

1. The impact of acute exacerbations of chronic pulmonary disease can be summarised as which of the following?
  - a) Acute exacerbations are associated with significant morbidity and mortality.
  - b) The patient's functional impairment may last several weeks.
  - c) Frequency of exacerbations is a good predictor of treatment failure.
  - d) All of the above.
  - e) None of the above.
2. The most common causes of acute exacerbations of COPD are:
  - a) Infectious process.
  - b) Allergic reactions.
  - c) Environmental factors.
  - d) All of the above.
  - e) None of the above.
3. The most common bacterial pathogens isolated in acute exacerbations of COPD are:
  - a) Nontypable *Haemophilus influenzae*.
  - b) *Streptococcus pneumoniae*.
  - c) *Moraxella catharralis*.
  - d) All of the above.
  - e) None of the above.
4. What factors are important to take into consideration when deciding how to treat patients with acute exacerbations of COPD?
  - a) The patient's age.
  - b) Smoking status.
  - c) Frequency of exacerbations.
  - d) Comorbidities.
  - e) All of the above.
5. In deciding what antibiotic to use in the treatment of acute exacerbations of COPD, which of the following characteristics of the drug do we need to consider?
  - a) Metabolism site.
  - b) Side-effects.
  - c) Drug interactions.
  - d) All of the above.
  - e) None of the above.
6. What of the following statements are correct in relation to acute exacerbations of COPD?
  - a) Viral and atypical pathogens are frequent cause of co-infection.
  - b) Viral infections result in a significant decrease in lung function.
  - c) Co-infections are frequent in acute exacerbations of COPD.
  - d) All of the above.
  - e) None of the above.

**Further reading**

White AJ, Gompertz S, Bayley DL, *et al*. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58: 680–685.

Christ-Crain M, Jaccard-Stolz D, Bingisser R, *et al*. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; 363: 600–607.

Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.

Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355.

Suggested answers  
1 d  
2 d  
3 a  
4 c  
5 d  
6 d