Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COPD Exacerbations

To X-ray or Not To X-ray

Exacerbations of COPD are a major cause of morbidity and mortality in patients with COPD. It is estimated that there are 16 million office visits, 500,000 hospitalizations, and 110,000 deaths attributed to COPD in the United States each year.[1,2] A great majority of the office visits are due to COPD exacerbations that are treated in the outpatient setting. Patients who are admitted to the ICU for COPD exacerbations have an in-hospital mortality of 24%.[3]

A diagnosis of COPD exacerbation is considered when there is increased dyspnea, increased sputum volume, and increased sputum purulence. Severity of an exacerbation can be quantified by assessing the magnitude of these three symptoms, as described by Anthonisen et al.[4] In a type 1 exacerbation, all three symptoms are present; in a type 2 exacerbation, any two of the three symptoms are present; and a type 3 exacerbation has only one symptom with any one of the following features: upper respiratory tract infection in the past 5 days, fever without cause, increased wheezing, cough, tachypnea, or heart rate of 20% above baseline. A chest radiograph is not done routinely in the outpatient setting unless pneumonia is suspected or if the patient is being considered for hospital admission based on the severity of initial symptoms. In two retrospective studies, chest radiograph abnormalities were reported in 16% of patients who were admitted to the hospital for COPD exacerbation.[5,6]

Airway infections of the tracheobronchial tree are responsible for the majority of exacerbations in COPD. Acute exacerbations are also associated with increased bronchial inflammation, as evidenced by influx of sputum neutrophils with elevated levels of myeloperoxidase and elastases along with increased levels of sputum cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor-α, and leukotriene B_4.[7,8] Approximately 50% of the exacerbations are caused by bacterial pathogens, 30% by viral infections, and the remaining exacerbations are caused by atypical pathogens and environmental allergen exposures. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the three most common bacterial pathogens, while Gram-negative bacilli like *Pseudomonas aeruginosa* may be involved in a subset of patients with more severe lung disease.[9] Atypical pathogens like *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may be responsible for $< 10\%$ of the exacerbations.[10]

The major goals for treatment of acute exacerbation of COPD are prompt improvement of symptoms with reduction in relapse rates and hospitalization. Treatment options for acute exacerbation of COPD include increased frequency of inhaled bronchodilators, use of oral steroids for 2 weeks in select patients, and antibiotics. Although the role of antibiotics has been questioned by some, results of 11 randomized controlled trials demonstrate a beneficial effect with the use of antibiotics in patients with moderate-to-severe COPD exacerbations.[11] The most commonly used antibiotics, also referred to as first- line antibiotics, include amoxicillin, trimethoprim-sulfamethoxazole, erythromycin, and doxycycline; while the newer antibiotics, referred to as second-line, broad-spectrum antibiotics, include the newer second-generation and third-generation cephalosporins, fluoroquinolones, extended spectrum macrolides, and β-lactamase–inhibitor combination.

Factors that are associated with poor treatment outcome include severity of underlying illnesses as judged by the type of exacerbation (type 1 vs type 3), type of pathogens with their susceptibility, and resistance patterns. Host factors include severity of airflow obstruction ($FEV_1 < 35\%$ of predicted), need for home oxygen, use of chronic steroid therapy, frequency of exacerbations (four or more per year), and presence of comorbid medical conditions such as congestive heart failure. The choice of antibiotics is generally guided by the severity of exacerbation, presence of risk factors, and the type of pathogens expected.[12,13] Several studies in the pre-1990s era did not show a difference in the treatment outcome based on the choice of antibiotics.[11] However, there is great concern over recent reports of increasing resistance to the most commonly used first-line antibiotics among the bacterial pathogens such as *H influenzae* and *S pneumoniae*.[14,15] In one retrospective study, the use of newer antibiotics reduced the failure and hospitalization rate when compared to first-line antibiotics.[16] In a second study, treatment with amoxicillin was associated with a higher failure rate when compared to other antibiotics.[17] In a prospective study, the use of ciprofloxacin as compared to the usual antibiotics, in patients with moderate-to-severe chronic bronchitis who had four or more exacerbations, was associated with improved outcome.[18] In general, the results of multiple studies demonstrate that patients who have lower FEV_1 values, who require more intensive therapy with bronchodilators and steroids, and patients who have not responded to treatment on prior

episodes of acute exacerbations are more likely to relapse within the next 14 to 30 days, as compared to patients with more favorable parameters.[11]

To optimize the treatment outcome, the Canadian Chronic Bronchitis Guidelines suggest stratifying patients with COPD exacerbations.[19] Patients with simple chronic bronchitis and no risk factors can be treated with the first-line, narrow-spectrum antibiotics, while patients with COPD with one or more risk factors can be treated with the newer, second-line antibiotics to reduce the odds of failure. Benefits of using a stratified treatment approach would allow the use of less expensive, narrow-spectrum antibiotics for patients with simple chronic bronchitis, while reserving the more expensive, second-line, broad-spectrum antibiotics for patients who are at greater risk for relapse or hospitalization. In a recent prospective trial, the use of ofloxacin demonstrated a significant benefit in the treatment of COPD exacerbations in patients requiring mechanical ventilation.[20] The selective use of second-line antibiotics could also limit the emergence of drug-resistant pathogens. Although there are no prospective randomized controlled trials to demonstrate that the Canadian guidelines are more effective than usual care, it makes intuitive sense that a stratified treatment approach that restricts the use of the newer broad-spectrum antibiotics is likely to be cost-effective and benefit patients with moderate-to-severe COPD exacerbations.

In this issue of *CHEST* (see page 1264), Lieberman et al compare and contrast the clinical presentations and infectious etiologies in 240 patients with pneumonic acute exacerbations (PNAE) and nonpneumonic acute exacerbations (NPAE) of COPD. All patients were admitted to the hospital and were prospectively studied. Twenty-three patients (10%) had PNAE, while the remaining 190 patients had NPAE. There were no differences in the demographic data, baseline spirometry, and arterial blood gas levels in stable state, use of chronic steroid therapy, rates of influenza and pneumococcal vaccination, and the presence of comorbidity between the two groups. Patients in the PNAE group had significantly higher rates of abrupt onset of illness, fever, and increased frequency of rales with more severe hypoxemia, as compared to the patients in NPAE group. Although clinically not significant, there was also a trend toward higher frequency of type 1 exacerbation (all three symptoms) in the PNAE group (70% vs 51%). Not surprisingly, the PNAE group had higher rates of admission to the ICU (26% vs 7%; $p < 0.006$), need for invasive ventilation (17% vs 5%; $p < 0.01$), hospitalization days (8.3 vs 4.1; $p < 0.001$), and higher mortality (13% vs 1%; $p < 0.007$), as compared to NPAE group.

There are several aspects of this study that are unique from other studies that merit discussion. First and foremost, this is the only study in the literature that has compared PNAE vs NPAE of COPD. Second, serology was the only diagnostic test that was used exclusively in this study for the diagnosis of the 12 pathogens (7 viral, 3 bacterial, and 2 atypical bacterial agents). Although blood cultures were done, sputum culture or other respiratory secretion cultures were not performed. Furthermore, the authors emphasize the virtues of serology in the diagnosis of pneumococcal infections, viral infections, and atypical bacterial pathogens in their study. The incidence of both viral and atypical pathogens was high in both the groups, despite the exclusion of common cold viruses (coronavirus and rhinovirus) and *C pneumoniae* infection due to technical difficulty with their assays. Perhaps the data from this study can be viewed in a different light. The use of serology offers an alternate option that is complimentary to conventional methods for making a diagnosis of these pathogens. However, the limitation of serology in the diagnosis of infectious causes is well recognized in the literature. Data from serologic tests are retrospective and are only useful in epidemiologic studies. Serology is generally not helpful in the prospective management of patients with community-acquired pneumonia and is not recommended by the American Thoracic Society guidelines.[21]

Third, an infectious etiology was identified in 96% of patients in the PNAE group as compared to 71% of patients in the NPAE group. This is clearly much higher than what is reported in most other conventional studies in patients with either community-acquired pneumonia or acute exacerbations of COPD. Both viral and bacterial etiologies were significantly higher in the pneumonic group. The significance of parainfluenzae virus type 2 and adenovirus in the PNAE group is not well understood. Fourth, the frequency of *H influenzae* and *M catarrhalis* infection, as reported by serology, was much lower in this study as compared to the literature. The authors acknowledge the limitation of serology in the diagnosis of these two pathogens and caution the readers about not making any therapeutic decisions based on the results of serology in their study. Fifth, the incidence of atypical pathogens (Legionella species, *M pneumoniae*) was similar between the two groups of patients. The results could have been different if *C pneumoniae* was included in the serology. Sixth, there was a high incidence of mixed pathogens in both the groups (59% vs 39%; p = not significant).

What conclusions can we draw from this study? Should patients with COPD exacerbations who demonstrate an infiltrate on a chest radiograph be

"lumped together" with patients without an infiltrate? The authors take a stand that the presence of an infiltrate on a chest radiograph in a patient with COPD should not be used to exclude them from a diagnosis of acute exacerbation of COPD for two reasons: (1) initial symptoms of increased dyspnea, increased sputum purulence, and volume cannot be used to differentiate clinically between the two groups except with a chest radiograph; and (2) the majority of the patients who are treated in the outpatient setting do not have a chest radiograph. However, one can argue that the presence of an infiltrate on the chest radiograph is the only key element that helps to differentiate between the two groups. The utility of a chest radiograph in a patient with suspected pneumonia is to confirm the clinical impression, determine the extent of radiographic involvement (unilobar vs multilobar), and identify any complications such as pleural effusion or bronchial obstruction. The results of their study, although small, clearly demonstrate worse outcomes in the PNAE group as compared to the NPAE group, with higher morbidity and mortality.

The authors also attempt to draw on some of the similarities between the two groups of patients with COPD, with and without pneumonia: the high rate of atypical bacterial pathogens and the absence of significant difference in the incidence of mixed infection. By emphasizing these similarities, they raise an important but "speculative question," whether similar approach to antibiotic therapy could be used in these two groups of patients with COPD exacerbations. Given the limitation of serology and because this study was not designed to address this issue, it is evident that no therapeutic decisions can be made based on the results of this study. Further studies designed to assess the type and frequency of infection by both serology and conventional respiratory cultures, along with documentation of the clinical risk factors and treatment outcomes, are required to address this issue. Until then, we should continue to obtain chest radiographs in patients with COPD exacerbations in whom pneumonia is suspected, or if they are being considered for hospital admission. Confirmation of an infiltrate on a chest radiograph warrants treatment approach as per American Thoracic Society guidelines for community-acquired pneumonia. The choice of antibiotics in patients with COPD exacerbations in the absence of pneumonia should be guided by the severity of exacerbation, the presence of risk factors, and expected bacterial pathogens with local susceptibility and resistance patterns.

Naresh A. Dewan, MBBS, MD, FCCP
Omaha, NE

Dr. Dewan is Chief, Pulmonary Section, Omaha VA Medical Center, and Professor, Department of Medicine, Creighton University.
Correspondence to: Naresh A. Dewan, MBBS, MD, FCCP, Pulmonary and Critical Care Division, Suite 3820, St. Joseph Hospital, 601 N 30th St, Omaha, NE 68131; e-mail: ndewan@creighton.edu

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ICU Echocardiography

Should We Use It in a Heart Beat?

> Ask, and it shall be given you; seek, and ye shall find; knock, and it shall be opened unto you.
>
> Matthew 7:7

In the current issue of *CHEST* (see page 1370), the report by Bossone and colleagues revealed a high incidence (36%) of occult cardiac abnormalities utilizing blinded comprehensive two-dimensional transthoracic echocardiography (TTE) and Doppler echocardiographic evaluation in 500 consecutive patients admitted to the University of Michigan medical ICU for noncardiac reasons. All of the TTE studies were obtained within 18 h of ICU admission. Approximately 14% of patients had two or more cardiac abnormalities identified. Only patients with a finding of pulmonary hypertension on TTE had a longer length of ICU stay, but there was no difference in mortality between patients with a positive finding on TTE and those with normal study findings. Patients with sepsis or liver failure as an ICU admitting diagnosis had a lower incidence of TTE findings, while patients with neurologic or hypertensive emergencies had a higher prevalence of abnormalities.

Like many well-designed, prospective blinded studies, this one raises as many questions as it answers. Of the 500 patients enrolled, 33 patients were removed. Two patients had inadequate studies, and 31 patients were determined to have a history of significant cardiovascular disease, or the current hospitalization represented an acute cardiovascular event. Fifty-two of 467 patients were unblinded for the incidental findings of a "critical" cardiovascular abnormality. Critical lesions were prospectively identified as severe valvular insufficiency or stenosis, right ventricular (RV) pressure ≥ 50 mm Hg, left ventricular (LV) ejection fraction $\leq 35\%$, pericardial effusion causing hemodynamic compromise, valvular vegetations, LV thrombus, or aortic dissection. It is open to speculation if these critical abnormalities would have been discovered eventually or if preemptively finding them impacted patient outcome. It is also unknown whether the findings in the 130 patients with cardiac abnormalities that were not revealed to the treating physicians would have changed management or outcome. Interestingly, there are no comparable studies measuring the incidence of cardiac abnormalities in surgical ICU patients, those admitted to a non-ICU hospital ward, or the general population.

On a daily basis in a medical-surgical ICU, we must evaluate and manage a wide variety of hypotensive or hemodynamically labile patients. Our clinical acumen, based on history, physical examination, laboratory, and radiographic evaluation, is often limited, and further data are needed.[1] Bossone et al reinforced the relative insensitivity of admission ECG combined with the portable chest radiograph in identifying TTE-determined cardiac findings. They also reported how infrequently TTE was ordered in patients who had cardiovascular abnormalities with findings that remained blinded to the investigators.

Unfortunately, Bossone and colleagues were not able to compare the utility of the pulmonary artery catheter (PAC) to the TTE in their diverse population with major medical illness. Routine use of the PAC has come into question because of the possible inaccuracy of pressure vs volume measurements, the lack of uniform and accurate interpretation of data acquired from the catheter, and concerns over excessive morbidity and mortality in patients who undergo catheterization.[2] Therefore, there are many times when a "snapshot" of cardiac function, like that provided by a noninvasive test such as a transthoracic echocardiogram, might be helpful. Poelaert et al[3] reported that 44% of patients with a PAC underwent a change in therapy after a transesophageal echocardiogram (TEE), showing that echocardiography can add to PAC measurements. There is ample evidence to suggest echocardiography can be helpful in dealing with the complex and dynamic patient in the ICU[4,5]; however there is inadequate information to guide intensivists on the utility, ease, and accuracy of TTE vs TEE. Bossone et al remind us that TEE may provide superior echocardiographic data.

Specially trained cardiologists independently interpreted all TTE studies in the study by Bossone