COPD Research Review™

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In this issue:

Abbreviations used in this issue:

AECOPD = acute exacerbation of COPD; **COPD** = chronic obstructive pulmonary disease; **CRP** = C-reactive protein; **FEV_1** = forced expiratory volume in 1s; **FVC** = forced vital capacity; **GOLD** = Global Initiative for Chronic Obstructive Lung Disease; **HR** = hazard ratio; **ICS** = inhaled corticosteroid.

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Welcome to the latest issue of COPD Research Review.

In this issue, Australian researchers evaluate the use of venous blood gases in the management of patients with AECOPD and type 2 respiratory failure, UK investigators report that CRP-guided treatment of COPD exacerbations in primary care reduces inappropriate antibiotic use, and several studies evaluate the use and prognostic significance of blood eosinophil counts in AECOPD. A Belgian study reports the benefits of long-term low-dose azithromycin in patients with AECOPD, German investigators find an increased mortality risk in COPD patients with chronic kidney disease, and a Chinese study highlights the harm associated with air pollution.

We hope you find these and the other selected studies interesting and welcome any feedback you may have.

Kind Regards,

Dr Philip Lee

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Role of venous blood gases in hypercapnic respiratory failure chronic obstructive pulmonary disease patients presenting to the emergency department

Authors: Wong E et al.

Summary: This Australian study examined the use of venous blood gas (VBG) measurements in patients with AECOPD and type 2 respiratory failure. 63 AECOPD patients with type 2 respiratory failure who presented to the emergency department and were being considered for non-invasive ventilation (NIV) were included. Arterial blood gases and VBGs were taken, and Bland-Altman plots were used for analysis. The limits of agreement for pH and HCO_3 in VBGs were narrow, but wider limits of agreement were noted for pCO_2.

Comment: NIV is effective in addressing respiratory acidosis due to acute hypoxic hypercapnic respiratory failure in COPD. Arterial sampling could be technically difficult and more painful than venous sampling. Previous studies have demonstrated good agreement between pH and HCO_3 values derived from venous and arterial blood gas sampling. This Australian pilot study again highlighted the utility of VBG in the assessment of pH and HCO_3. VBG is less painful than arterial blood gases with lower risk of bruising. Although VBG should not be considered as a replacement of arterial blood gases in assessing the severity of respiratory failure or monitoring treatment response to NIV, it could potentially expedite the assessment of acute COPD exacerbations via early identification of acute hypercapnic respiratory failure, allowing prompt NIV establishment.

Reference: Intern Med J 2019;49(7):834-7

Abstract

C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations

Authors: Butler C et al.

Summary: This open-label study evaluated the use of point-of-care CRP testing to guide antibiotic prescribing in patients with AECOPD. 653 patients who presented to general practices in England and Wales for AECOPD were assigned to receive usual care guided by CRP point-of-care testing (CRP-guided group) or usual care alone (usual-care group). Fewer patients in the CRP-guided group than in the usual-care group received an antibiotic prescription at the initial consultation (47.7% vs 69.7%) and during the first 4 weeks of follow-up (59.1% vs 79.7%). The Clinical COPD Questionnaire total score at 2 weeks favoured the CRP-guided group.

Comment: Although the majority of COPD exacerbations are viral in origin, antibiotics are often prescribed for secondary bacterial respiratory tract infections, especially in patients with increased sputum volume and discolouration. This UK study utilised CRP to determine if antibiotic prescribing could be rationalised without compromising clinical outcomes in primary care. It found the proportion of COPD patients receiving antibiotics was significantly lower in the CRP-guided group than the usual-care group. Of note, clinical outcomes including self-reported health status and need for hospitalisation were similar in the two groups. CRP-guided treatment of COPD exacerbations in primary care appears useful in reducing inappropriate antibiotic use and should be incorporated in routine COPD management.

Reference: N Engl J Med 2019;381:111-20

Abstract

Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease

Authors: Pascoe S et al.

Summary: This analysis of the global IMPACT trial evaluated the effect of blood eosinophil counts and smoking status on treatment response in patients with COPD. The IMPACT trial compared once daily single-inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol) with dual inhaled therapy (fluticasone furoate/vilanterol or umeclidinium/vilanterol) in patients with moderate to very severe COPD and ≥1 moderate or severe exacerbation in the past year. The magnitude of benefit of ICS-containing regimens in reducing rates of moderate and severe exacerbations (compared with a non-ICS dual long-acting bronchodilator regimen) increased in proportion to blood eosinophil count. Smoking status modified the relationship between observed efficacy and blood eosinophil count for moderate or severe exacerbations.

Comment: ICS has a limited role in the treatment of COPD. Previous studies have demonstrated that the risk of COPD exacerbations increases with blood eosinophil counts. The utility of blood eosinophil count and smoking status was again demonstrated in this study. COPD patients with higher blood eosinophil counts had the greatest benefit from ICS therapy. Therefore, in the latest GOLD guidelines, it is proposed that eosinophil count <100 cells/µl and >300 cells/µl could identify patients who may receive little or no benefit and those who may receive the greatest benefit from ICS therapy.

Reference: Lancet Respir Med 2019: published online Jul 4
Abstract

Azithromycin during acute COPD exacerbations requiring hospitalization (BACE)

Authors: Vermeersch K et al.

Summary: This Belgian study investigated the use of long-term, low-dose azithromycin in patients hospitalised with AECOPD. 301 patients were randomised within 48h of hospitalisation for AECOPD to receive azithromycin 500 mg/day or placebo for 3 days in addition to standard acute treatment with systemic corticosteroids and antibiotics. Low-dose azithromycin (250mg every 2 days) was subsequently continued for 3 months. Treatment failure was defined as the composite of treatment intensification with medication, step-up in hospital care, readmission for respiratory reasons, or all-cause mortality. The treatment failure rate at 3 months was lower in the azithromycin group than in the placebo group (49% vs 60%; p=0.0526). Clinical benefits were no longer evident 6 months after treatment cessation.

Comment: Azithromycin reduces the frequency of COPD exacerbations and improves quality of life but at the expense of causing hearing decrements in a small percentage of patients. This Belgian study reviewed the addition of azithromycin to systemic corticosteroids and antibiotics, commencing with 3 days of 500mg daily, followed by 250mg every 2 days for a total of 3 months. Due to premature termination of recruitment, statistical significance for the primary outcome (time to first event analysis using treatment failure rate within 3 months) was not reached. However, intensive care length of stay was reduced in the azithromycin group and the benefit of preventing exacerbation by azithromycin was reduced over the next 6 months after cessation of therapy, suggesting that azithromycin therapy needs to be administered on a longer-term basis. The contemplated mechanism of action for macrolide therapy is its anti-inflammatory effect. However, owing to the concern of macrolide resistance, targeting COPD patients with the highest risk of exacerbation and identifying the appropriate phenotype would be paramount.

Reference: Am J Respir Crit Care Med 2019; published online May 3
Abstract

Effectiveness and safety of inhaled corticosteroids in older individuals with COPD and/or asthma

Authors: Kendzerska T et al.

Summary: This longitudinal population study investigated the use of ICS in older adults with asthma or COPD (or features of both) in a real-word setting. 238,283 patients aged ≥66 years in Ontario, Canada, who had COPD and/or asthma in 2003–2014 were followed until March 2015 using provincial health administrative data. 87,690 patients had asthma (27% with concurrent COPD) and 150,593 had COPD (25% with concurrent asthma). ICS use was associated with fewer obstructive lung disease hospitalisations in patients with asthma alone (HR, 0.84); but concurrent COPD attenuated the benefit. A similar association was seen in patients with COPD and concurrent asthma (HR, 0.88), but not in those with COPD alone. ICS receipt was associated with a marginally increased risk of pneumonia hospitalisations in patients with COPD and no asthma (HR, 1.03), but not in the other groups.

Comment: Benefits of ICS in asthma are well established, including improvement of symptoms/lung function, reduced airway hyper-responsiveness and frequency of exacerbations. Potential benefits of ICS therapy in COPD include reduced likelihood of acute clinical deterioration/exacerbation in patients with a history of repeated exacerbations or hospitalisation. This Canadian population study found ICS use in older adults with asthma or concomitant asthma/COPD was associated with fewer obstructive lung disease hospitalisations. However, ICS had little impact on hospitalisations with an increased risk of pneumonia-related hospitalisations in older adults with COPD. Under current guidelines, ICS is not indicated for patients with COPD who are being initiated on pharmacotherapy, except those with coexisting asthma. ICS should not be prescribed for patients with COPD in whom the risks of ICS outweigh the benefits.

Reference: Ann Am Thorac Soc 2019; published online Jul 12
Abstract

Combined forced expiratory volume in 1 second and forced vital capacity bronchodilator response, exacerbations, and mortality in chronic obstructive pulmonary disease

Authors: Fortis S et al.

Summary: The American Thoracic Society (ATS) defines a positive bronchodilator response (ATS-BDR) as a composite of an FEV_1 and/or FVC increase of ≥12% and 200ml. This analysis of the COPDGene study examined whether ATS-BDR components are differentially associated with clinical and functional features in COPD. Of 3340 COPD patients included in the analysis, 32.43% had ATS-BDR, 5.45% had FEV_1-BDR, 15.63% had FVC-BDR, and 11.34% had combined-BDR. All BDR categories were associated with FEV_1 decline compared with no-BDR. Both ATS-BDR and combined-BDR were associated with higher functional residual capacity and greater 6-minute-walk distance than no-BDR. In contrast to ATS-BDR, combined-BDR was independently associated with less emphysema, more frequent exacerbations and severe exacerbations, and lower mortality.

Comment: Spirometry can assist in differentiating between asthma and COPD. Airflow limitation in COPD is not fully or substantially reversible after bronchodilation, whereas the airflow limitation in asthma is usually fully reversible after bronchodilation. Of note, positive bronchodilator response with FEV_1 or FVC response between 200ml and 400ml (or ≥12%) could be found in asthma or COPD. This study utilised data from the COPDGene study and assessed the pattern of bronchodilator response and the association with clinical phenotype/outcome in COPD patients, excluding patients with a self-reported history of asthma. Significant bronchodilator response is defined as an increase of at least 12% and 200ml in FEV_1 or FVC. It showed that positive bronchodilator response was associated with higher functional residual capacity and greater 6-minute walk distance. Combined FEV_1 and FVC bronchodilator response was associated with less extent of emphysema on imaging, more frequent and severe COPD exacerbations and lower mortality rates. COPD patients with significant bronchodilator response may have a similar clinical phenotype to asthma. Significant bronchodilator response does not imply the patient has COPD/asthma overlap, as positive bronchodilator response can frequently occur in COPD. Therefore, it will be necessary to review the history and pattern of respiratory symptoms.

Reference: Ann Am Thorac Soc 2019;16(7):826-35
Abstract

References: 1. ULTIBRO® BREEZHALER® 110/50 Approved Product Information. February 2018. **2.** Wedzicha JA *et al. Lancet Respir Med* 2013;1:199–209. **3.** Wedzicha JA *et al. N Engl J Med.* 2016; 374:2222-2234. **4.** Seretide® Approved Product Information. **5.** Spiriva® Approved Product Information. **6.** Spiriva® Respimat® Approved Product Information.

Low and high blood eosinophil counts as biomarkers in hospitalized acute exacerbations of COPD

Authors: MacDonald M et al.

Summary: This Australian study evaluated whether blood eosinophil counts predict treatment response in patients with AECOPD. 341 patients hospitalised with AECOPD were included. Patients were grouped according to blood eosinophil count, ranging from low (<50/µl) to high (>150/µl). Exacerbations were considered to be associated with infection if virus testing was positive or CRP level was ≥20 mg/L. Low blood eosinophil count was found to be more strongly associated with infection (91% vs 51.9%; p=0.001), longer hospital stays (median 7 vs 4 days; p<0.001), and lower 12-month survival (82.4% vs 90.7%; p=0.028) than high blood eosinophil count.

Comment: Blood eosinophil counts may serve as a biomarker for exacerbation risk in COPD. Previous studies have identified high bacterial loads and higher rates of pneumonia in COPD patients with low blood eosinophil counts. This Australian cohort study supported such findings and highlighted that low eosinophil counts (<50/µl) were associated with infection with longer hospital stays and reduced survival, when compared with COPD patients with high eosinophil counts (>150/µl). Use of blood eosinophil counts to predict COPD outcomes should be combined with clinical assessment of exacerbation risk, as indicated by the history of exacerbations.

Reference: Chest 2019;156(1):92-100
Abstract

Incidence of type II diabetes in chronic obstructive pulmonary disease

Authors: Gayle A et al.

Summary: This nested case-control study used primary care data from the Clinical Practice Research Datalink (CPRD) to investigate the incidence of type 2 diabetes mellitus (T2DM) in patients with COPD. 220,971 COPD patients with smoking history registered at a CPRD practice in 2010–2016 were matched 1:5 with patients by age, gender and general practice. The incidence rate of T2DM in COPD patients was 1.26 per 100 patient-years, and was higher among men than women (1.32 vs 1.18 per 100 patient-years). Logistic regression analysis adjusted for confounding factors found that the odds ratio for T2DM was 1.47 in frequent exacerbators versus infrequent exacerbators, and 1.73 in patients receiving high-dose ICS versus no ICS.

Comment: ICS use in COPD is associated with significant adverse health effects, including significantly increased risks for pneumonia and diabetes. This UK cohort study showed that T2DM incidence amongst COPD patients was high. ICS exposure and frequent COPD exacerbations are associated with a higher risk of T2DM in COPD patients. Therefore, careful assessment of the risk-benefit balance is warranted before introducing ICS to any COPD inhaled bronchodilator therapy. Cessation of unnecessary ICS should be considered in patients without any clinical evidence of coexisting asthma and those without frequent exacerbations, as the risks would outweigh the benefits.

Reference: NPJ Prim Care Respir Med 2019;29(1):28
Abstract

Independent commentary by Dr Philip Lee, MBBS (Hons) FRACP.
Dr Philip Lee is a Respiratory and Sleep Physician currently working at the St. George Hospital Centre for Sleep Disorders & Respiratory Failure in Sydney. His research interests include non-invasive ventilation, respiratory failure and sleep disordered breathing.

Consequences of chronic kidney disease in chronic obstructive pulmonary disease

Authors: Trudzinski F et al.

Summary: This analysis of the German COPD and Systemic Consequences – Comorbidities Network (COSYCONET) cohort examined the impact of chronic kidney disease (CKD) in patients with COPD. CKD was diagnosed if patients had estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2. The effect of CKD on comorbidities, symptoms, physical capacity and St George's Respiratory Questionnaire were evaluated. 2274 patients were included in the analysis, 161 of whom had CKD. Spline models adjusted for confounding factors revealed independent associations between eGFR and modified British Medical Research Council dyspnoea scale, St George's Respiratory Questionnaire, 6-minute walk test, and timed up and go test. CKD was also independently associated with increased mortality (HR, 2.3; p<0.001).

Comment: CKD is a common comorbidity amongst COPD patients. This German cohort study included 161 patients with concomitant CKD/COPD. It showed that their mortality rate was significantly higher than that of patients with COPD alone. COPD patients with CKD were at higher risk for mortality, independent of other cardiovascular comorbidities. Of note, functional status and exercise capacity were also compromised amongst COPD patients with CKD. The real-world COPD prevalence in CKD patients could be significantly higher than in this study and vigilance regarding respiratory symptoms in CKD patients is paramount.

Reference: Respir Res 2019;20(1):151
Abstract

Effect of ambient air quality on exacerbation of COPD in patients and its potential mechanism

Authors: Yan P et al.

Summary: This Chinese study evaluated the effects of ambient air quality in COPD patients. 139 patients with COPD who lived in Beijing during the summer and temporarily migrated to Sanya City in the winter were included. Air pollution, as measured by air quality index, was significantly worse in Beijing during summer than in Sanya during winter (1613.1 vs 49.4; p<0.001). The COPD Assessment Test score was significantly higher in Beijing than in Sanya (26.4 vs 20.0; p=0.019), as was the Modified Medical Research Council dyspnoea scale (2.9 vs 1.9; p<0.001). FEV_1 was significantly better when patients were in Sanya than when they were in Beijing (48.88% vs 41.79%; p<0.01). The relative risks of hospitalisation and acute exacerbation in Beijing compared with Sanya were 1.64 and 3.36, respectively.

Comment: Previous research demonstrated the link between air pollution (particulate matter) and increased mortality/hospitalisation in COPD patients. This Chinese study isolated a group of COPD patients moving from Beijing (a city with a relatively higher burden of air pollution in summer) to Sanya in winter where air pollution is considered less severe than Beijing. It was postulated that air pollutant particle matters induce apoptosis of airway epithelial cells. It showed a higher symptom burden, relative risk of hospitalisation and acute exacerbation amongst patients residing in Beijing with significant FEV_1 improvement when they moved to Sanya. COPD patients are susceptible to the acute effects of air pollution.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:1517-26
Abstract

