with oxygen-driven bronchodilator administration.[1346]

Glucocorticoids

Data from studies (mostly hospital based) indicate that systemic glucocorticoids in COPD exacerbations shorten recovery time and improve lung function (FEV1). They also improve oxygenation,[1347-1350] the risk of early relapse, treatment failure,[1351] and the length of hospitalization.[1347,1349,1352] A dose of 40 mg prednisone-equivalent per day for 5 days is recommended.[1353] One observational study suggests that longer courses of oral corticosteroids for COPD exacerbations are associated with an increased risk of pneumonia and mortality.[1354] Therapy with oral prednisolone is equally effective to intravenous administration.[1355] Nebulized budesonide alone may be a suitable alternative for treatment of exacerbations in some patients,[1348,1356,1357] and provides similar benefits to intravenous methylprednisolone, although the choice between these options may depend on local cost issues.[1358,1359] Even short bursts of corticosteroids are associated with subsequent increased risk of pneumonia, sepsis and death[1360] and use should be confined to patients with significant exacerbations. Recent studies suggest that glucocorticoids may be less efficacious to treat acute COPD exacerbations in patients with lower levels of blood eosinophils[487,1320,1323,1361] and more trials of steroid-sparing treatment regimens are required. A double-blind, placebo-controlled RCT (STARR2) of prednisolone therapy guided by blood eosinophil count during acute COPD exacerbation found that this strategy was non-inferior to standard care including systematic prednisolone treatment (30 mg per day for 14 days) and allowed a 33% reduction in the proportion of patients receiving prednisolone.[1362] The study authors concluded that blood eosinophil-directed prednisolone can be used to safely reduce systemic glucocorticoid use in clinical practice.[1362]

Antibiotics

Although the infectious agents in COPD exacerbations can be viral or bacterial,[1311,1363] the use of antibiotics in exacerbations remains controversial.[352,1364,1365] The uncertainties originate from studies that did not differentiate between bronchitis (acute or chronic) and COPD exacerbations, studies without placebo-control, and/or studies without chest X-rays that do not exclude that patients may have had underlying pneumonia. There is evidence supporting the use of antibiotics in exacerbations when patients have clinical signs of a bacterial infection e.g., increased sputum purulence.[352,1365] Indeed, the use of observed sputum color can safely modulate antibiotic therapy with no adverse effects if sputum is white or clear in color. On the other hand, observed sputum purulence has 94.4% sensitivity and 52% specificity for high bacterial load, indicative of a causative relationship.[352]

A systematic review of placebo-controlled studies has shown that antibiotics reduce the risk of short-term mortality by 77%, treatment failure by 53% and sputum purulence by 44%.[1366] The review provides evidence to treat moderately or severely ill patients with COPD exacerbations and increased cough and sputum purulence with antibiotics.[1366,1367] These data are supported by more RCTs in patients with diagnoses of moderate COPD.[1368] In an RCT, the addition of doxycycline to oral corticosteroid an outpatient setting did not prolong time to next exacerbation.[1369] In the outpatient setting, sputum cultures are not feasible as they take at least two days and frequently do not give reliable results for technical reasons. Several biomarkers of airway infection are being studied in exacerbations of COPD that have a better diagnostic profile. Earlier studies of C-reactive protein (CRP) have reported contradictory findings.[1370,1371] A randomized trial found a marked reduction in antibiotic prescriptions without impaired outcomes in UK primary care outpatients with ECOPD in whom antibiotics prescriptions were guided by point-of-care CRP testing.[1372] Another trial in patients hospitalized for exacerbations of COPD in The Netherlands found similar results (reduced antibiotic use with no increase in treatment failure). These findings need confirmation in other settings before a recommendation to generalize this approach. However, data has indicated that antibiotic usage can be safely reduced from 77.4% to 47.7% when CRP is low.[1373]

Procalcitonin is an acute phase reactant that increases in response to inflammation and infection and has been studied to determine the use of antibiotics in COPD exacerbations.[1374] The efficacy of this biomarker is controversial. Several studies, mainly done in the outpatient setting, suggested that procalcitonin-guided antibiotic treatment reduces