Antibiotics in acute exacerbations of chronic obstructive pulmonary disease

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Physicians in office-based practices write more antibiotic prescriptions for respiratory tract infections than for any other condition. Because of the controversy surrounding the efficacy of such prescriptions, however, asking the questions "Does my patient require an antibiotic?" and "If so, which one, at what dose, and for how long?" has become a difficult undertaking. And before writing a prescription we also need to consider potential drug side effects or interactions, patient allergies, and patients' ability to pay for medications.

In this issue of *Canadian Family Physician,* Korbila et al[1] take us back in time to reconsider which first-line agents are best for acute bacterial exacerbations of chronic bronchitis (ABECB)—penicillins or trimethoprim-based regimens? Before pondering this issue, it is crucial to ensure we are talking about the same condition.

What's in a name?

As a respirologist, I tend to be very "black and white" in my categorization of respiratory tract infections. What exactly is the clinical difference between acute bronchitis (AB), community-acquired pneumonia (CAP), and ABECB? I add acute exacerbations of chronic obstructive pulmonary disease (AECOPD), the preferred Canadian term, to this list because in this context it is interchangeable with the term ABECB.

Almost everyone has had an episode of "acute bronchitis." It is a self-limiting illness in individuals with healthy lungs and its most common symptoms are cough, wheeze, and sputum that might be coloured. Patients with AB, however, do not benefit from antibiotics; a pivotal randomized controlled trial showed no difference in symptom improvement between azithromycin and vitamin C.[2]

Therefore we are practising appropriate "antibiotic stewardship" when patients with AB leave without antibiotic prescriptions. In contrast, physicians should never knowingly fail to prescribe antibiotics for a patient with CAP. Community-acquired pneumonia comprises a constellation of signs and symptoms, which include cough, sputum, localized physical signs on chest auscultation, and fever. The diagnosis is confirmed by the presence of new or progressive infiltrate on chest x-ray scans. Although most patients can be treated safely as outpatients, we need to be vigilant for those with sepsis and end-organ dysfunction—which presents as hypotension, confusion, a respiratory rate of more than 30 breaths per minute—as they might require emergency triage and hospital admission.

Cases of ABECB and AECOPD also almost always require antibiotic treatment. They occur predominately in current or ex-smokers who have already been diagnosed with COPD; ABECB and AECOPD are about 20 times more common than CAP.

Exacerbation or normal variation?

The natural course of COPD includes repeated acute exacerbations, with frequency rising to between 1 and 4 episodes per year in severe COPD. Between 3% and 16% of such exacerbations require hospitalization, and among severe episodes, mortality is as high as 10%.[3] Although AECOPD can mostly be managed in primary care, elderly patients or those with substantial comorbidities require more vigilance on our part. These patients will have chronic bronchitis—that is, daily cough productive of sputum on most days for 3 months cumulatively in 2 consecutive years—rather than emphysema, which causes chronic breathlessness and is usually not complicated by infectious exacerbations.

Most patients with chronic bronchitis in a stable state cope well despite substantial limitations and various comorbidities. An acute infection, however, (usually viral and perhaps picked up while visiting grandchildren) can be enough to cause considerable deterioration in symptoms and tip patients into respiratory failure.

How do we determine if a patient is presenting with an acute exacerbation rather than normal, day-to-day variation of chronic bronchitis or COPD symptoms?

A very well-designed, double blind, randomized, crossover trial conducted in the early 1980s in Winnipeg, Man, helped us find the answer.[4] Patients with AECOPD were given amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline, or a corresponding placebo. Those taking antibiotics who returned with further exacerbations subsequently received the placebo, and vice versa. Patients who did not receive an antibiotic in this study deteriorated and required hospitalization twice as often as those who received antibiotics. The authors discovered that patients with 2 or more of the following symptoms—known as the Anthonisen criteria—benefit from a broad-spectrum antibiotic: increased dyspnea, increased sputum production, and increased sputum purulence (ie, change in colour).

A systematic review of subsequent randomized, placebo-controlled trials has shown a small benefit for AECOPD patients receiving antibiotics rather than

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placebo (although each of the original study groups had only a small number of patients).[5]

Management guidelines

Various guideline groups from around the world have integrated all of the evidence surrounding AECOPD management. Although the basic approach of all the guidelines is similar, the Canadian ones lead the world by encouraging risk stratification of patients to guide antibiotic selection.[3,6]

The Global Obstructive Lung Disease guidelines[7] and the European Respiratory Society guidelines[8] have minor differences but they both note that the antibiotic of choice should be an aminopenicillin, a macrolide, or a tetracycline. Quinolones have performed equally well in clinical trials, but they have not yet been universally accepted to have clinical superiority over other antibiotics.

Use of TMP-SMX has fallen out of favour, mainly owing to a very public campaign in the United Kingdom about the rare but life-threatening side effect of Stevens-Johnson syndrome. Questions were raised about why seniors in Brighton, England, were dying of side effects from TMP-SMX.[7] This led the Committee of Safety of Medicines to write to all practitioners in the United Kingdom advising them to limit TMP-SMX to prophylaxis for and treatment of *Pneumocystis carinii* in immunocompromised individuals. This was accompanied by a nationwide media frenzy. Although the committee subsequently backed down, mainly because of the extensive use of TMP-SMX for urinary tract infections, it continued to restrict its use in ABECB. Patients are now extremely reluctant to accept prescriptions for TMP-SMX.

While evidence supports antibiotic use in AECOPD, pathogens are becoming increasingly resistant. This is particularly true of the 2 main pathogens in COPD, *Moraxella catarrhalis* and *Haemophilus influenzae*. They are currently 100% and 36% β-lactamase-producing, respectively, and this substantially limits penicillin's effectiveness.

The Canadian guidelines state that penicillin or TMP-SMX should only be given to patients with mild COPD who have not had previous exacerbations and who have no comorbid illnesses.[3] For patients with COPD who are receiving chronic corticosteroid therapy and who have frequent exacerbations or comorbid illnesses, such as diabetes or cardiovascular disease, the guidelines call for respiratory fluoroquinolones or amoxicillin-clavulanate, owing to the high levels of resistance and failure of first-line agents. Ciprofloxacin is best reserved for those at risk of or with proven *Pseudomonas aeruginosa* infection.

It is also important to inquire about recent use of antibiotics and to integrate the concept of antibiotic cycling into practice. Rather than simply increasing the dose or prolonging the duration of therapy, physicians should change the class of antibiotics if patients have received antibiotics for any reason in the past 3 months.

For those with more severe presentations, there is excellent evidence for addition of oral prednisone at 30 to 50 mg daily for 10 days, with no need to taper.[9] This adjuvant therapy reduces hospital stays by about 1 day among admitted patients and reduces unscheduled physician visits or return to urgent care among those treated but discharged from emergency departments. Although there is no solid office-based study, Canadian guidelines suggest a similar short course of oral steroids for those patients who present with a history of severe COPD or who are at risk of deterioration.

Chronic disease management model

It is crucial to adopt a chronic disease management model for patients who have had exacerbations. Following successful treatment of acute exacerbations, follow-up should be arranged. These visits should be used to ensure patients are managing COPD appropriately to optimize current function and quality of life and to prevent further exacerbations. Allied health professionals can also provide education on symptom reduction and encourage smoking cessation, influenza and pneumococcal vaccinations, and appropriate nonpharmacologic and pharmacologic interventions, along with referral for specialist assessment as appropriate.[10,11]

The burden of COPD is increasing. Patients with exacerbations are frequent visitors to emergency departments and are among those most frequently admitted to general medical wards. It is important not to become complacent about this common condition; we must integrate the most recent guidelines into our practices.

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Competing interests

Dr McIvor has received honoraria for continuing medical education and attending advisory board meetings from Abbott, Bayer, Boehringer Ingelheim, GlaxoSmithKline, and Pfizer.

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