Amoxicillin + clavulanic acid

Essential medicine status

ATC codes: J01CR02

Indication	Chronic obstructive pulmonary disease with acute exacerbation ICD11 code: CA22.0
INN	Amoxicillin + clavulanic acid
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	**Parenteral > General injections > IV:** 500 mg (as sodium salt) + 100 mg (as potassium salt) powder for injection ; 1000 mg (as sodium salt) + 200 mg (as potassium salt) powder for injection **Oral > Solid > tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt)
EML status history	First added in 2017 (TRS 1006) Changed in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Amoxicillin + clavulanic acid
DrugBank	Amoxicillin , Clavulanic acid (Clavulanate)

Expert Committee recommendation

The Expert Committee noted that antibiotics are not required in all patients presenting with COPD exacerbations. The Committee endorsed the inclusion on the EML of amoxicillin and amoxicillin + clavulanic acid as first-choice therapy and of cefalexin and doxycycline as second-choice therapy for use in suspected bacterial exacerbations of COPD.

Background

Exacerbations of chronic obstructive pulmonary disease (COPD) are an important health-care burden. Although treatment can involve bronchodilators and anti-inflammatory agents, including steroids, antimicrobials are frequently used on the basis that a bacterial infection is suspected of acting as a trigger to the episode. However, antibiotics are indicated in only a minority of patients presenting with exacerbated COPD (see guidelines summaries below).

Summary of evidence

The highest-quality review was a 2012 Cochrane review (16 randomized controlled trials (RCTs); 2068 participants) (1). There was no significant benefit in using antibiotics compared with not using antibiotics in outpatients when treatment was restricted to available antibiotics (risk ratio (RR) 0.80; 95% confidence interval (CI) 0.63–1.01) but there was evidence of benefit for inpatients (RR 0.77; 95% CI 0.65–0.91). In contrast, an older and lower-quality systematic review (9 RCTs; 1101 patients) found a small clinical benefit with antibiotic treatment but provided no further details of the population who benefited (2). Similarly, a systematic review from 2008 (10 RCTs; 959 participants) found higher treatment failure rates with placebo than with antibiotic treatment overall (RR 0.54; 95% CI 0.32–0.92) and in hospitalized patients (RR 0.34; 95% CI 0.20–0.56) but not ambulatory patients (RR 0.88; 95% CI 0.56–1.39) (3). In-hospital mortality was also found to be lower with antibiotic treatment (RR 0.22;

95% CI 0.08–0.62). These reviews did not compare antibiotics. Of two reviews that compared different antibiotic agents, one compared first- and second-line antibiotics (12 RCTs; 2261 participants) and reported that first-line antibiotics (amoxicillin, ampicillin, pivampicillin, sulfamethoxazole + trimethoprim, and doxycycline) were associated with lower treatment success than second-line agents (amoxicillin + clavulanic acid, macrolides, second- or third-generation cephalosporins, and quinolones) (odds ratio (OR) 0.51; 95% CI 0.34–0.75 (4). Interpretation of these findings was difficult, however, since specific classes of antibiotics were not compared separately, i.e. no head-to-head comparisons were provided, and many of the antibiotics considered second-line in this review are nowadays considered to be first-line agents. The second review (5 RCTs; 287 participants), found no differences in treatment success, adverse events or mortality between patients treated with penicillins and those treated with sulfamethoxazole + trimethoprim but did not meet the applicant's criteria for non-inferiority (5). In terms of duration of treatment, one systematic review (21 RCTs; 10 698 participants) compared the outcome for short-duration treatment (up to 5 days) with longer durations (6). With reasonably small confidence intervals, the authors found no difference in efficacy (RR 0.99; 95% CI 0.90–1.08 for clinical cure at the 4-week mark). This was confirmed by another systematic review from the same year, which included fewer studies (7). In summary, the evidence from RCTs was insufficient for the applicants to recommend one antibiotic or class of antibiotics over another; guidelines therefore informed the choices of antibiotics for the EML. Limiting the duration of treatment to 5 days was supported by appreciable evidence.

Guidelines

The 2004 American Thoracic Society (ATS) and European COPD guidelines recommend that antibiotics for outpatient treatment may be initiated if there are altered sputum characteristics (8). Amoxicillin/ampicillin, doxycycline, azithromycin, clarithromycin, dirithromycin, roxithromycin, levofloxacin and moxifloxacin were potential candidates, depending on local bacterial resistance patterns. For hospitalized patients, amoxicillin + clavulanic acid, respiratory fluoroquinolones (levofloxacin and moxifloxacin), and combination therapy were recommended if Pseudomonas and other Gram-negatives were suspected. National Institute for Health and Care Excellence (NICE) guidelines recommend antibiotics only if there is purulent sputum or clinical or radiographic evidence of pneumonia in which case an aminopenicillin, a macrolide or a tetracycline could be used, taking into account local resistant patterns (9). Canadian guidelines distinguish acute tracheobronchitis, which does not need antibiotic treatment, from chronic bronchitis with and without risk factors (complicated), and chronic suppurative bronchitis (10). For chronic bronchitis without risk factors, macrolides, second- and third generation cephalosporins, amoxicillin, doxycycline, and sulfamethoxazole + trimethoprim are recommended. In complicated bronchitis (with risk factors), fluoroquinolones and beta-lactams/beta lactamase inhibitors are recommended. In chronic suppurative bronchitis, targeted treatment of the identified pathogen is recommended. The U.S. Food & Drug Administration (FDA) published a boxed warning against the use of fluoroquinolones for this indication because of side-effects associated with antibiotics of this class (11). The main concerns related to disabling and potentially permanent adverse effects on tendons, muscles and joints, and to peripheral neuropathy and central nervous system effects, also reported in otherwise healthy patients. The FDA continues to recommend the use of fluoroquinolones in life-threatening infections where the potential benefit outweighs the risk.

Rationale for antibiotic selection

Based on the guidelines, amoxicillin – alone or in combination with clavulanic acid – and a cephalosporin (cefuroxime or cefalexin) were proposed as core antibiotics providing appropriate coverage. Clarithromycin and doxycycline are alternatives if beta-lactams or cephalosporins cannot be used. Azithromycin was not proposed as an alternative to clarithromycin because of safety concerns. Dirithromycin and roxithromycin were not proposed as they offer no benefit compared with clarithromycin, which is also recommended for other syndromes. Sulfamethoxazole + trimethoprim was not proposed as it was listed in only one of the guidelines and is not frequently used for this indication. Because of the side-effect profile of fluoroquinolones and the emergence of resistance, levofloxacin should be used only if no better options among the antibiotics listed here are available. Moxifloxacin was not proposed as it is not considered to be superior to levofloxacin, and levofloxacin is listed for several other indications. COPD is a disease of the adult patient population and it was therefore not surprising that no systematic review data or guidelines were found for management in the paediatric population. No treatment recommendations were made for paediatric patients.

Committee considerations

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML. As a result, cefuroxime, clarithromycin and levofloxacin were excluded since other narrower-spectrum options were available. Recommended first- and second-choice antibiotics are

reported above. First-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML recommendations: Chronic obstructive pulmonary disease with acute exacerbation

First choice	Second choice
amoxicillin	cefalexin
amoxicillin + clavulanic acid	doxycycline

1. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;(12):CD010257.
2. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA. 1995;273(12):957–60.
3. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2008;133(3):756–66.
4. Dimopoulos G, Siempos, II, Korbila IP, Manta KG, Falagas ME. Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials. Chest. 2007;132(2):447–55.
5. Korbila IP, Manta KG, Siempos, II, Dimopoulos G, Falagas ME. Penicillins vs trimethoprim-based regimens for acute bacterial exacerbations of chronic bronchitis: meta-analysis of randomized controlled trials. Can Fam Physician. 2009;55(1):60–7.
6. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. Thorax. 2008;63(5):415–22.
7. Falagas ME, Avgeri SG, Matthaiou DK, Dimopoulos G, Siempos II. Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother. 2008;62(3):442–50.
8. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–46.
9. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. London: National Institute for Health and Care Excellence; 2010 (Clinical Guideline CG101; https://www.nice.org.uk/guidance/cg101, accessed 26 March 2017).
10. Balter MS, La Forge J, Low DE, Mandell L, Grossman RF. Canadian guidelines for the management of acute exacerbations of chronic bronchitis: executive summary. Can Respir J. 2003;10(5):248–58.
11. Fluoroquinolone antibacterial drugs for systemic use: Drug Safety Communication - warnings updated due to disabling side effects. Silver Spring, MD: U.S. Food & Drug Administration; 2016 (https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm513065.htm, accessed 26 March 2017).