Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing

NICE guideline

Draft for consultation July 2018

This guideline sets out an antimicrobial prescribing strategy for acute exacerbations of chronic obstructive pulmonary disease (COPD). It aims to optimise antibiotic use and reduce antibiotic resistance.

See a 2-page visual summary of the recommendations, including tables to support prescribing decisions.

Who is it for?

- Healthcare professionals
- People with COPD, their families and carers

The guideline contains:

- the draft recommendations
- summary of the evidence.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the full evidence review, details of the committee and any declarations of interest.

Recommendations

The recommendations in this guideline are for the use of antibiotics for managing an acute exacerbation of chronic obstructive pulmonary disease (COPD). See the NICE guideline on COPD (2010) for other recommendations on preventing and managing an acute exacerbation of COPD, including self-management. For managing other lower respiratory tract infections, see the NICE antimicrobial prescribing guidelines on acute exacerbation of

bronchiectasis, acute cough (including acute bronchitis), community-acquired pneumonia and hospital-acquired pneumonia, and the NICE guideline on pneumonia in adults: diagnosis and management.

1.1 Managing an acute exacerbation of COPD with antibiotics

1.1.1 Be aware that an acute exacerbation of COPD is a sustained worsening of symptoms from a person's stable state.

1.1.2 Be aware that a range of factors (including viral infections and smoking) can trigger an acute exacerbation of COPD and many exacerbations are not caused by bacterial infections so will not respond to antibiotics (see the NICE guideline on COPD).

Treatment

1.1.3 Offer an antibiotic (see the recommendations on choice of antibiotic) for people with a severe acute exacerbation of COPD.

1.1.4 Consider an antibiotic for people with an acute exacerbation of COPD that is not severe, but only after taking into account:

- the number and severity of symptoms, bearing in mind that for people with less severe or fewer symptoms who are having treatment in the community there is evidence of uncertain benefit of antibiotics
- whether they need to go into hospital for treatment (see the NICE guideline on COPD)
- previous exacerbation and hospital admission history, and the risk of developing complications
- previous sputum culture and susceptibility results
- the risk of antimicrobial resistance with repeated courses of antibiotics.

1.1.5 If a sputum sample has been sent for culture and susceptibility testing (in line with the NICE guideline on COPD) and an antibiotic prescription has been given:

- review the choice of antibiotic when microbiological results are available, **and**
- only change the antibiotic according to susceptibility results if bacteria are resistant and symptoms are not already improving (using a narrow spectrum antibiotic wherever possible).

1.1.6 If no antibiotic prescription is given, give advice about:

- an antibiotic not being needed currently
- seeking medical help without delay if symptoms such as increased sputum production or change in sputum colour worsen rapidly or significantly, do not start to improve after an agreed time, or the person becomes systemically very unwell.

1.1.7 If an antibiotic prescription is given, give advice about:

- possible adverse effects of the antibiotic, particularly diarrhoea
- seeking medical help if symptoms worsen rapidly or significantly at any time, or the person becomes systemically very unwell.

Reassessment

1.1.8 Reassess the person if symptoms worsen rapidly or significantly at any time, taking account of:

- other possible diagnoses, such as pneumonia
- any symptoms or signs suggesting a more serious illness or condition, such as cardiorespiratory failure or sepsis
- previous antibiotic use which may have led to resistant bacteria.

Send a sputum sample for culture and susceptibility testing if symptoms have not resolved following antibiotic treatment and this has not been done already.

Referral and seeking specialist advice

1.1.9 Refer people with an acute exacerbation of COPD to hospital:

- if they have a severe systemic infection, **or**
- if they have any of the high risk criteria for severe illness or death from the NICE guideline on sepsis
- and in line with the NICE guideline on COPD for treatment of an exacerbation.

1.1.10 Seek specialist advice for an acute exacerbation of COPD if the person:

- has symptoms that are not improving with repeated courses of antibiotics
- has bacteria that are resistant to oral antibiotics
- cannot take oral medicines (to explore locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital where appropriate).

See the evidence and committee discussion on antibiotics.

1.2 Choice of antibiotic

1.2.1 When prescribing antibiotic treatment for an acute exacerbation of COPD follow table 1 for adults aged 18 years and over.

1.2.2 Give oral antibiotics first-line if the person can take oral medicines, and the severity of their exacerbation does not require intravenous antibiotics.

1.2.3 Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible.

Table 1. Antibiotic treatment for adults aged 18 years and over

Antibiotic[1]	**Dosage and course length**[2]
First choice oral antibiotics[3,4,5]	
Amoxicillin	500 mg three times a day for 5 days

Doxycycline	200 mg on first day, then 100 mg once a day for 5-day course in total
Clarithromycin	500 mg twice a day for 5 days
Erythromycin	500 mg four times a day for 5 days
Second choice oral antibiotics (no improvement in symptoms on first choice taken for at least 2 to 3 days [or other agreed time]; guided by susceptibilities when available)[4,5]	
Use alternative first choice (from a different class)	as above
Alternative choice oral antibiotics if severely unwell or higher risk of resistance (guided by susceptibilities when available)	
Co-amoxiclav	500/125 mg three times a day for 5 to 7 days
Levofloxacin	500 mg once daily for 5 to 7 days
Moxifloxacin	400 mg once daily for 5 to 7 days
Co-trimoxazole[6]	960 mg twice a day for 5 to 7 days
First choice intravenous antibiotic (if unable to take oral antibiotics; guided by susceptibilities when available)[5,7]	
Co-amoxiclav	1.2 g three times a day
Azithromycin	500 mg once daily
Clarithromycin	500 mg twice daily
Co-trimoxazole[6]	960 mg to 1,440 mg twice a day
Second choice intravenous antibiotic	
Consult local microbiologist; guided by susceptibilities	

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding.

[2] Doses given are by mouth using immediate-release medicines, unless otherwise stated.

[3] Empirical treatment or guided by most recent sputum culture and susceptibility.

[4] Amoxicillin or erythromycin are the preferred choices in women who are pregnant.

[5] Where a person is receiving prophylactic antibiotics, treatment should be with an antibiotic from a different class.

[6] Co-trimoxazole should only be considered for use in acute exacerbations of COPD when there is bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic (BNF, June 2018).

[7] Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible.

See the evidence and committee discussion on choice of antibiotic and antibiotic course length.

Terms used in the guideline

Acute exacerbation of COPD

An exacerbation is a sustained worsening of the person's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour (NICE guideline on COPD [2010]).

Severity of exacerbation

A general classification of the severity of an acute exacerbation (NICE guideline on COPD [2010]; Oba Y et al. [2017]) is:

- mild exacerbation: the person has an increased need for medication, which they can manage in their own normal environment
- moderate exacerbation: the person has a sustained worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics
- severe exacerbation: the person experiences a rapid deterioration in respiratory status that requires hospitalisation.

Anthonisen et al. (1987) classified the type of an acute exacerbation based on 3 cardinal exacerbation symptoms:

- increased breathlessness,
- increased sputum volume, and
- sputum purulence.

The presence all 3 symptoms was defined as type 1 exacerbation; 2 of the 3 symptoms was defined as type 2 exacerbation; and 1 of the 3 symptoms with the presence of 1 or more supporting symptoms and signs was defined as type 3 exacerbation. This classification has been widely used to determine the severity of exacerbation in research, with more symptoms indicating a more severe exacerbation.

Supporting symptoms were:

- cough
- wheezing
- fever without an obvious source

- upper respiratory tract infection in the past 5 days
- respiratory rate increase and/or heart rate increase 20% above baseline.

Summary of the evidence

The recommendations in this guideline are based on the evidence identified, which was for antibiotics for managing an acute exacerbation of COPD in adults. Non-antimicrobial interventions, such as bronchodilators, corticosteroids and oxygen therapy are covered in the NICE guideline on COPD (2010).

Antibiotics

- A number of factors are known to trigger an acute exacerbation of COPD, such as a viral respiratory tract infection and environmental factors, such as smoking (see the NICE guideline on COPD). Only about half of exacerbations are thought to be caused by a bacterial infection (Vollenweider et al. 2012).
- The diagnosis of COPD or chronic bronchitis varied across included studies, and may have been confirmed by spirometry or by a clinician. It was not defined in some studies.
- Similarly, the diagnosis of an acute exacerbation varied, but was mainly based on the Anthonisen classification or a clinical evaluation of worsening symptoms and signs. In some studies it was not defined.
- Studies often included people with varying severity of acute exacerbation (often based on the Anthonisen classification of type of exacerbation or not defined). Studies were conducted in various settings.

Back-up antibiotics

- No systematic reviews or randomised controlled trials (RCTs) were identified on back-up antibiotics for people with an acute exacerbation of COPD.

Efficacy of antibiotics

- The evidence review for the efficacy of antibiotics was based on a systematic review and meta-analysis of RCTs (Vollenweider et al. 2012).

This systematic review conducted subgroup analyses by care setting, and a sensitivity analysis restricted to antibiotics which the authors considered to be in current use.

- With antibiotics, significantly fewer people (age range 52 to 72 years) with an acute exacerbation of COPD failed to resolve or have improved exacerbation symptoms up to 1 month after treatment starting, compared with placebo (28.4% versus 37.4%, number needed to treat [NNT] 12 [range 8 to 23], very low quality evidence).
- However, this was a heterogeneous population of people treated in the community, in hospital or in intensive care, and the result was influenced by the large positive effect observed in 1 RCT in an intensive care population. When this study was removed from the analysis, the benefit of antibiotics compared with placebo was reduced (29.4% versus 36.1%, NNT 15 [range 9 to 50], moderate quality evidence).
- The diagnosis of an acute exacerbation was a worsening of previously stable COPD, with 1 or more symptoms such as increased breathlessness, increased cough, increased sputum volume or change in sputum colour. The care setting was used a marker of the severity of the acute exacerbation.
- A wide range of antibiotics were included across the studies and the antibiotic course length ranged from 5 to 17 days. Corticosteroid treatment was allowed in 2 of the 16 RCTs.
- Significantly fewer people who were treated with antibiotics failed to resolve or have improved exacerbation symptoms compared with placebo. The effect of antibiotics appeared to be greater in people with increasing severity of exacerbation (based on care setting), as follows:
  - in people treated in the community (classified as a mild to moderate exacerbation): 19.9% versus 27.5%, NNT 14 (range 8 to 46), moderate quality evidence
  - in people treated in hospital (classified as a severe exacerbation): 41.8% versus 52.0%, NNT 10 (range 6 to 45, moderate quality evidence)

  - in people treated in intensive care (classified as a very severe exacerbation): 10.6% versus 56.5%, NNT 3 (range 2 to 4), high quality evidence.
- Vollenweider et al. (2012) also conducted a sensitivity analysis which only included antibiotics that the authors considered to be in current use (including amoxicillin, co-amoxiclav, co-trimoxazole and doxycycline). Studies assessing oxytetracycline, tetracycline and chloramphenicol were excluded from this analysis. There remained a significant difference between antibiotics and placebo overall in this analysis (24.5% versus 34.5%; NNT 11 [range 7 to 21, low quality evidence), but there was no significant difference in a subgroup of people treated in the community (22.2% versus 29.1%, low quality evidence) or in people treated in hospital (excluding intensive care: 28.9% versus 45.9%, low quality evidence).
- Antibiotics were not significantly more effective than placebo in reducing the length of hospital stay in 3 RCTs that reported this outcome (11 days versus 17 days, very low quality evidence). Antibiotics significantly reduced the number of days off work during follow-up in people treated in the community in 1 RCT, although this was based on small numbers of participants (n=88) and a short follow-up period (17 days) (4.3 days versus 9.4 days, high quality evidence, Vollenweider et al. 2012).

Safety of antibiotics

- Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE Clinical Knowledge Summary [CKS]: diarrhoea – antibiotic associated).
- Allergic reactions to penicillins occur in 1 to 10% of people and anaphylactic reactions occur in less than 0.05%. People with a history of atopic allergy (for example, asthma, eczema and hay fever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics (BNF, June 2018). See the NICE guideline on drug allergy for more information.
- Co-trimoxazole is currently under restriction for use in the UK. It is advised that it only be considered for use in acute exacerbations of COPD when

there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibiotic (BNF, June 2018).

- From the systematic review and meta-analysis of RCTs (Vollenweider et al. 2012), adverse events were significantly increased with antibiotics compared with placebo between 5 and 28 days after treatment (10.6% versus 7.4%, low quality evidence), although there is considerable uncertainty in this result as the frequency of adverse events was low. Significantly more people reported diarrhoea with antibiotics compared with placebo (4.4% versus 1.8%, low quality evidence), although the incidence was low in both groups.
- See the summaries of product characteristics for information on contraindications, cautions and adverse effects of individual medicines.

Committee discussion on antibiotics

Limitations of the data:

- The committee discussed the evidence from a large systematic review and meta-analysis of double-blind, placebo-controlled RCTs for the use of antibiotics in people with an acute exacerbation of COPD (Vollenweider et al. 2012).
- The committee noted the variations in diagnosis of COPD (or chronic bronchitis) and acute exacerbations of COPD across the included studies (particularly in older studies). The included studies covered a heterogeneous population ranging from people with mild exacerbations treated in the community to people with very severe exacerbations requiring ventilation in intensive care. There was no definition for the severity of exacerbation that was used in the studies.
- The committee questioned the appropriateness of using the care setting as a proxy for the severity of exacerbation (many included studies were from the US where hospital admission systems differ from UK practice).
- Evidence that is available from RCTs in the systematic review does not help to identify people who have a bacterial infection and may be more likely to benefit from an antibiotic. The committee noted, and agreed with

the authors conclusions, that in the analysis there was a lack of power to determine clinical effectiveness by the presence or absence of particular symptoms or signs (for example, purulent sputum). The committee also noted that the systematic review included people who presented with 1 or more exacerbation symptom, and the analysis did not stratify people by symptoms when assessing the effectiveness of antibiotics.

- The committee agreed that microbiological eradication outcomes were difficult to interpret and that clinical outcome measures should be prioritised, although they recognised that the definition of treatment failure (no improvement) varied across the studies.
- The committee also noted the analysis based on antibiotics in current use, and agreed that these results should be prioritised for decision-making.

Interpretation of the results

- Overall, the committee noted reasonably high NNTs for antibiotics compared with placebo. In people who were treated in the community, about 14 people would need to be treated with antibiotics to prevent 1 person from having treatment failure (no improvement in symptoms). In people who were treated in hospital, about 10 people would need to be treated with antibiotics to prevent 1 person from having treatment failure.
- When antibiotics not currently used in practice were excluded from the analysis, the differences between antibiotics and placebo were not statistically significant in the sub-group analyses by care setting (community and hospital). However, the committee agreed that this may be because of a lack of power when fewer studies were included in the analysis. Also not all the antibiotics considered to be in current use by the authors are in current use in the UK.
- Overall, the evidence did not identify populations who may benefit most from antibiotics, but antibiotics appeared to be more effective with increasing severity of exacerbation symptoms (when care setting was used as a proxy for the severity of exacerbation). The committee noted

that the NNT for failure to improve was 3 in people treated in intensive care.

- The committee agreed that the limited benefit was likely to be because many acute exacerbations are not caused by a bacterial infections, but may be caused by viral infections or environmental factors, such as smoking.

Rationale for decision-making

- The committee acknowledged the recommendations in the NICE guideline on COPD which cover managing acute exacerbations, including self-management. This guideline focuses on optimising the use of antibiotics for an acute exacerbation of COPD and minimising the risk of antimicrobial resistance.
- Based on experience, the committee agreed that many health professionals may not be aware of the limited benefit of antibiotics, and that many exacerbations are not caused by a bacterial infection.
- The committee agreed that the evidence suggested that antibiotics had uncertain clinical benefit in a heterogeneous population of people with acute exacerbations of COPD, in the context of increased harms with antibiotics and antimicrobial resistance.
- However, the committee agreed, based on the evidence that people with severe exacerbations should be offered an antibiotic. In the study, people with severe exacerbations were treated in hospital and those with very severe exacerbations were treated in an intensive care unit.
- In people with acute exacerbations that are not severe, the committee agreed that the limitations of the evidence made it more difficult to develop recommendations. The committee recognised that COPD is a complex condition and people often have multiple exacerbations and receive multiple courses of antibiotics, which may not always be appropriate.
- From experience, the evidence identified and the need to minimise the risk of antimicrobial resistance, the committee agreed that an antibiotic should only be considered for people with an acute exacerbation of

COPD that is not severe on an individual patient basis. This should take into account the uncertain benefit of antibiotics and the risk of antimicrobial resistance with repeated courses, balanced against the number and severity of their symptoms, their need for hospital treatment, their exacerbation and hospitalisation history, their risk of complications, and previous sputum culture results.

- The committee noted that many studies were based on the Anthonisen classification, which shows the more cardinal symptoms a person has, the more likely they are to benefit from an antibiotic. However, available evidence was not able to conclude which people were more likely to benefit from an antibiotic by using specific clinical symptoms or signs (for example, purulent sputum).
- From experience, the committee recognised that a person's condition may change rapidly during an acute exacerbation. It agreed that health professionals should give the person individualised advice about seeking medical help without delay if symptoms worsen rapidly or significantly, do not start to improve after an agreed time, or they become systemically very unwell.
- The committee was aware of recommendations from NICE guidelines on COPD and sepsis that cover when to refer people to hospital.

Choice of antibiotics

First-line antibiotics compared with second-line antibiotics

- Evidence for the choice of first-line or second-line antibiotics was based on a systematic review and meta-analysis of RCTs (Dimopoulos et al. 2007).
- First-line antibiotics (amoxicillin, ampicillin, pivampicillin, co-trimoxazole and doxycycline) were significantly less effective in resolving or improving exacerbation symptoms up to 7 days after the end of treatment, compared with second-line antibiotics (co-amoxiclav, macrolides, quinolones and cefaclor) in people (age range 49 to 71 years) with an acute exacerbation of chronic bronchitis (81.8% versus 91.3%, NNT 11 [range 8 to 16], moderate quality evidence).

- Similar results were observed in a subgroup of people who were treated in the community with first-line and second-line antibiotics respectively (90.3% versus 95.5%, moderate quality evidence), although most people in both groups had resolving or improving exacerbation symptoms up to 7 days after the end of treatment. In people treated in hospital, there was no significant difference between first-line and second-line antibiotics (74.0% versus 87.5%, low quality evidence), but some studies also included people treated in the community.
- Dimopoulos et al. (2007) included 4 RCTs in people treated in the community and 6 RCTs in people treated in hospital (4 of these RCTs had a mixed population who were treated in the community or in hospital).
- The diagnosis of an acute exacerbation and the type of symptoms was based on the Anthonisen classification. The severity of exacerbation varied across studies and was not specified in 2 RCTs.
- Dosage varied by antibiotic and the course length ranged from 5 to 14 days. Corticosteroid treatment was permitted before an acute exacerbation in 3 RCTs.
- There were no significant differences between groups in antibiotic-related adverse events (14.6% versus 20.6%, very low quality evidence) or in all-cause mortality (1.0% versus 1.6%, low quality evidence).

Other antibiotic comparisons

- There were no significant differences in clinical effectiveness between antibiotics or classes of antibiotics, including co-amoxiclav, macrolides, quinolones, cephalosporins and trimethoprim (with or without a sulphonamide) in people with an acute exacerbation of COPD. This is based on 2 systematic reviews and meta-analyses of RCTs (Korbila et al. 2009 and Siempos et al. 2007) and 4 RCTs (Nouira et al. 2010, Petitpretz et al. 2007, Yoon et al. 2013, and Urueta-Robledo et al. 2006), which all cover different comparisons of antibiotic regimens for up to 6 months (in 2 RCTs) follow-up.
- One large systematic review and meta-analysis of 19 RCTs (Siempos et al. 2007, n=7,045) comparing commonly used broader spectrum antibiotics (co-amoxiclav, macrolides and quinolones) for 3 to 10 days found no

significant difference in clinical effectiveness between groups (moderate to high quality evidence). The majority of people included in this review were treated in the community. The available data did not allow subgroup analyses to be carried out in people considered to be at increased risk of poorer outcomes (such as older people, people with severe COPD and people with more frequent exacerbations).

- Diagnosis of acute exacerbation varied across the studies, but was mainly based on Anthonisen classification or a clinical evaluation of symptoms and signs. In some studies it was not defined.
- The severity of an acute exacerbation also varied across the studies, but was based on the Anthonisen classification of type of exacerbation or was not defined. Some studies were carried out only in people with a severe exacerbation, and in some cases sub-group analyses were performed based on the severity of the person's exacerbation.
- In Siempos et al. (2007), a subgroup analysis of people with moderate or severe acute exacerbations found no significant difference in the resolution or improvement in exacerbation symptoms between macrolides and quinolones (80.7% versus 80.1%, high quality of evidence).
- In 1 double-blinded RCT (Nouira et al. 2010; n=170) the effectiveness of co-trimoxazole 160/800 mg twice daily for 10 days was compared with ciprofloxacin 750 mg twice daily for 10 days in people (mean age 67 years) with a severe acute exacerbation of COPD being admitted to an intensive care unit in hospital. No significant differences between antibiotic groups were found up to 6 months after treatment (low to moderate quality evidence).
- The antibiotic course length ranged from 3 to 14 days in the studies. One double-blinded RCT (Urueta-Robledo et al. 2006) found no significant difference in the resolution of exacerbation symptoms with levofloxacin for 7 days compared with moxifloxacin for 5 days (moderate quality evidence).
- Overall, there were no major differences in adverse effects between antibiotics or classes of antibiotics based on the included studies (low to high quality evidence)

- In the systematic review by Siempos et al. (2007), significantly more people reported adverse events with co-amoxiclav compared with quinolones (16.6%% versus 12.8%, NNH 27 [range 13 to 207], moderate quality evidence).

Committee discussion on choice of antibiotic

- Although there was some evidence to suggest that second-line antibiotics were more effective than first-line antibiotics, the absolute difference between groups was small and this analysis was limited by the classification of first- and second-line antibiotics which was not consistent with current UK practice.
- Based on evidence of no major differences in clinical effectiveness between antibiotics or classes of antibiotics, the committee agreed that the choice of antibiotic should largely be driven by minimising the risk of resistance.
- If an antibiotic is given, the committee agreed that this should be started empirically or based on the most recent sputum culture (if available). The committee was aware that the NICE guideline on COPD (2010) makes the following recommendations about when to send sputum for culture.
  - For people who have their exacerbation managed in primary care, sending sputum samples for culture is not recommended in routine practice.
  - In people with an exacerbation referred to hospital, it is recommended that a sample should be sent for microscopy and culture if sputum is purulent.
  - Sputum culture is also recommended to identify organisms if sputum is persistently present and purulent.
- The committee agreed that if a sputum sample has been sent for culture and susceptibility testing, when results are available, if they suggest the bacteria are not susceptible, the person should be contacted to assess symptoms. However, the antibiotic should only be changed according to susceptibility results if symptoms are not already improving. In line with

good antimicrobial stewardship, narrow spectrum antibiotics should be used wherever possible, and antibiotics switched from intravenous to oral where applicable.

- Based on experience, common pathogens in acute exacerbations of COPD, the susceptibility of these to various classes of antibiotics, the risks of resistance, and good antimicrobial stewardship, the committee agreed antibiotic choices as described below. Several oral and intravenous antibiotics were recommended as people with acute exacerbations of COPD may have repeated courses of antibiotics and may be at an increased risk of resistance. It also enables antibiotics to be selected based on the severity of illness and antibiotic susceptibilities from culture results (if available).
- The first-line **oral antibiotics** are **amoxicillin** (a penicillin), **doxycycline** (a tetracycline) and **clarithromycin** or **erythromycin** (in pregnancy), which are macrolides, used at the usual doses for an acute exacerbation of COPD. These antibiotics have good activity against common pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae.* Amoxicillin or erythromycin are preferred in women who are pregnant. Where a person is receiving prophylactic antibiotics, treatment should be with an antibiotic from a different class.
- The second-line **oral antibiotics** for people whose symptoms worsen on a first-choice antibiotic taken for at least 2 to 3 days (or other agreed time) are an alternative first-choice from a different antibiotic class (a different antibiotic may be used for a subsequent exacerbation). This allows broader-spectrum antibiotics (some of which also have additional safety warnings) to be reserved for people who are severely unwell or at a higher risk of resistance.
- The alternative **oral antibiotics** for people who are severely unwell or at higher risk of resistance (guided by susceptibilities when available) are:
  - **co-amoxiclav** 500/125 mg three times a day; this broad-spectrum antibiotic combines a penicillin with a beta-lactamase inhibitor, making it active against beta-lactamase-producing bacteria that are resistant to amoxicillin alone

  - **co-trimoxazole** 960 mg twice a day (trimethoprim plus a sulphonamide); which is suitable only for people with bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic
  - **levofloxacin** 500 mg once daily or **moxifloxacin** 400 mg once daily (quinolones), which are the quinolones used in the studies.
- First-choice **intravenous antibiotics** at usual doses for treating acute exacerbations in people who are unable to take oral antibiotics are:
  - **co-amoxiclav** (a penicillin with a beta-lactamase inhibitor)
  - **azithromycin** or **clarithromycin** (macrolides)
  - **co-trimoxazole**
- Second-choice intravenous antibiotics may be needed for some people after specialist advice, based on the severity of illness, likely pathogens or antibiotic susceptibilities from culture results when available, and local resistance patterns.
- The committee agreed that a sputum sample should be sent for culture and susceptibility testing if symptoms have not resolved following antibiotic treatment and this has not been done already. Specific organisms, such as *Pseudomonas aeruginosa* may need to be looked for if people have prolonged recurrent exacerbations. They discussed that some people with resistant bacteria may need intravenous antibiotics, particularly if they are not responding to several courses of oral antibiotics for the same episode, or if several sputum samples show resistance to oral antibiotics.
- The committee discussed that specialist advice should be sought for people needing intravenous antibiotics, to discuss local options for giving intravenous antibiotics at home or in the community, rather than in hospital.

Antibiotic course length

- Short-course antibiotics (for less than 6 days) were not significantly different from long-course antibiotics (for 7 days or more of the same

antibiotic) in resolution of exacerbation symptoms after completing treatment, in people with an acute exacerbation of COPD (moderate quality evidence). This was based on a systematic review and meta-analysis (Stolbrink et al. 2017). This result was consistent regardless of the length of follow-up (within 6 days, 7–14 days or more than 20 days) or the care setting (3 of the 10 RCTs were in hospital).

- The diagnosis of an acute exacerbation was based on clinical evaluation in all studies, except 1 RCT that used microscopically confirmed purulent sputum. The severity of exacerbation ranged from mild to severe, and 4 RCTs used the Anthonisen classification of type of exacerbation for assessing exacerbation severity.
- A range of antibiotics were included in Stolbrink et al. (2017) with quinolones being the most commonly studied antibiotics. In most studies a 3-day or 5-day course was compared with a 7-day or 10-day course of the same antibiotic.
- There were significantly fewer adverse events with short-course antibiotics compared with long-course antibiotics (20.9% versus 24.9%, NNH 25 [range 14 to 100]; low quality evidence).
- No systematic reviews or RCTs were identified that compared the frequency of antibiotic dosing or the route of antibiotic administration.

Committee discussions on antibiotic course length

- The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and minimise the risk of adverse effects.
- Based on the evidence, if an antibiotic was prescribed, the committee agreed that a 5-day course of all the recommended antibiotics was required to treat an acute exacerbation. However, they did acknowledge that some people who are more severely ill may need a 7-day course.
- In line with the NICE guideline on antimicrobial stewardship and Start smart – then focus, the committee agreed that the use of intravenous antibiotics should be reviewed by 48 hours (taking into account the

person's response to treatment and susceptibility results from sputum culture) and switched to oral treatment where possible.

Other considerations

Medicines adherence

- Medicines adherence may be a problem for some people with medicines that require regular dosing (for example, some antibiotics) (see the NICE guideline on medicines adherence).

Resource implications

- Recommended antibiotics are all available as generic formulations, see Drug Tariff for costs.

See the full evidence review for more information.