NICE National Institute for Health and Care Excellence

Public Health England

NICE guideline

Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing

NICE guideline

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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guideline should be read in conjunction with NG115.

Overview

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.

See the NICE guideline on COPD in over 16s for other recommendations on preventing and managing an acute exacerbation of COPD, including self-management.

Who is it for?

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

Recommendations

1.1 Managing an acute exacerbation of COPD with antibiotics

1.1.1 Be aware that:

- an acute exacerbation of chronic obstructive pulmonary disease (COPD) is a sustained worsening of symptoms from a person's stable state
- a range of factors (including viral infections and smoking) can trigger an exacerbation
- many exacerbations (including some severe exacerbations) are not caused by bacterial infections so will not respond to antibiotics
- some people at risk of exacerbations may have antibiotics to keep at home as part of their exacerbation action plan (see the recommendations on choice of antibiotic).

  See the NICE guideline on COPD in over 16s.

Treatment

1.1.2 Consider an antibiotic (see the recommendations on choice of antibiotic) for people with an acute exacerbation of COPD, but only after taking into account:

- the severity of symptoms, particularly sputum colour changes and increases in volume or thickness beyond the person's normal day-to-day variation
- whether they may need to go into hospital for treatment (see the NICE guideline on COPD in over 16s)
- 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.

1.1.3 If a sputum sample has been sent for culture and susceptibility testing (in line with the NICE guideline on COPD in over 16s) and an antibiotic has been given:

- review the choice of antibiotic when 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).

1.1.4 If an antibiotic is given, give advice:

- about possible adverse effects of the antibiotic, particularly diarrhoea
- that symptoms may not be fully resolved when the antibiotic course has been completed
- about seeking medical help if:
  - symptoms worsen rapidly or significantly **or**
  - symptoms do not start to improve within 2 to 3 days (or other agreed time) **or**
  - the person becomes systemically very unwell.

1.1.5 If no antibiotic is given, give advice about:

- an antibiotic not being needed currently
- seeking medical help without delay if:
  - symptoms (such as sputum colour changes and increases in volume or thickness) worsen rapidly or significantly **or**
  - symptoms do not start to improve within an agreed time **or**
  - the person becomes systemically very unwell.

Reassessment

1.1.6 Reassess people with an acute exacerbation of COPD if their 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 improved following antibiotic treatment and this has not been done already.

Referral and seeking specialist advice

1.1.7 Refer people with an acute exacerbation of COPD to hospital if they have any symptoms or signs suggesting a more serious illness or condition (for example, cardiorespiratory failure or sepsis) and in line with the NICE guideline on COPD in over 16s.

1.1.8 Seek specialist advice for people with an acute exacerbation of COPD if they:

- have symptoms that are not improving with repeated courses of antibiotics **or**
- have bacteria that are resistant to oral antibiotics **or**
- 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).

For a short explanation of why the committee made these recommendations, see the evidence and committee discussion on antibiotics.

Full details of the evidence and the committee's discussion are in the evidence review.

1.2 Choice of antibiotic

1.2.1 When prescribing an antibiotic 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

Treatment	Antibiotic, dosage and course length
First-choice oral antibiotics (empirical treatment or guided by most recent sputum culture and susceptibilities)	**Amoxicillin**: 500 mg three times a day for 5 days (see the BNF for amoxicillin dosage in severe infections) **Doxycycline**: 200 mg on first day, then 100 mg once a day for 5-day course in total (see the BNF for doxycycline dosage in severe infections) **Clarithromycin**: 500 mg twice a day for 5 days
Second-choice oral antibiotics (no improvement in symptoms on first choice taken for at least 2 to 3 days; guided by susceptibilities when available)	Use alternative first choice (from a different class)

Treatment	Antibiotic, dosage and course length
Alternative choice oral antibiotics (if person at higher risk of treatment failure; guided by susceptibilities when available)	**Co-amoxiclav**: 500/125 mg three times a day for 5 days **Co-trimoxazole**: 960 mg twice a day for 5 days **Levofloxacin** (with specialist advice if co-amoxiclav or co-trimoxazole cannot be used; consider safety issues): 500 mg once a day for 5 days
First-choice intravenous antibiotics (if unable to take oral antibiotics or severely unwell; guided by susceptibilities when available)	**Amoxicillin**: 500 mg three times a day (see the BNF for amoxicillin dosage in severe infections) **Co-amoxiclav**: 1.2 g three times a day **Clarithromycin**: 500 mg twice a day **Co-trimoxazole**: 960 mg twice a day (see the BNF for co-trimoxazole dosage in severe infections) **Piperacillin with tazobactam**: 4.5 g three times a day (see the BNF for piperacillin with tazobactam dosage in severe infections)
Second-choice intravenous antibiotics	Consult a local microbiologist; guided by susceptibilities

See the BNF for appropriate use and dosing in specific populations, for example, in hepatic impairment, renal impairment, and when administering intravenous antibiotics.

If a person is having antibiotic prophylaxis, treatment should be with an antibiotic from a different class.

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

People who may be at a higher risk of treatment failure include people who have had repeated courses of antibiotics, a previous or current sputum culture with resistant bacteria, or people at higher risk of developing complications.

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, co-trimoxazole, October 2018).

See the Medicines and Healthcare products Regulatory Agency advice for restrictions and precautions for using fluoroquinolone antibiotics due to very rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems. Warnings include: stopping treatment at first signs of a serious adverse reaction (such as tendonitis), prescribing with special caution in people over 60 years and avoiding coadministration with a corticosteroid (March 2019).

For a short explanation of why the committee made these recommendations, see the evidence and committee discussion on choice of antibiotics and antibiotic course length.

Full details of the evidence and the committee's discussion are in the evidence review.

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 in over 16s).

Severity of exacerbation

A general classification of the severity of an acute exacerbation (NICE guideline on COPD in over 16s and 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
- 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 studies, 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 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 chronic obstructive pulmonary disease (COPD) in adults. Non-antimicrobial interventions, such as bronchodilators, corticosteroids and oxygen therapy are covered in the NICE guideline on COPD in over 16s.

Antibiotics

- A number of factors are known to trigger an acute exacerbation of COPD, including a viral respiratory tract infection and environmental factors, such as smoking (see the NICE guideline on COPD in over 16s). 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 of type of exacerbation 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 had symptoms that didn't resolve or improve 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 receiving treatment in the community, in hospital or in intensive care, and the result was influenced by the large positive effect observed in 1 RCT in people in intensive care. 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 had antibiotics had symptoms that didn't resolve or improve 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 receiving treatment 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 receiving treatment in hospital (classified as a severe exacerbation): 41.8% versus 52.0%, NNT 10 (range 6 to 45), moderate quality evidence
  - in people receiving treatment 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 receiving treatment in the community (22.2% versus 29.1%, low quality evidence) or in people receiving treatment 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 receiving treatment in the community in 1 RCT, although this was based on small numbers of participants (n=88) and a short follow-up (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 on diarrhoea – antibiotic associated).
- About 10% of the general population claim to have a penicillin allergy; this is often because of a skin rash that occurred while taking a course of penicillin as a child. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. See the NICE guideline on drug allergy for more information.
- People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics (BNF, phenoxymethylpenicillin, October 2018).
- Macrolides should be used with caution in people with a predisposition to QT interval prolongation (BNF, clarithromycin, October 2018).
- Tendon damage (including rupture) has been reported rarely in people receiving fluoroquinolones (BNF, October 2018), and the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (EMA press release October 2018) has recommended restricting the use of these antibiotics following a review of disabling and potentially long-lasting side effects mainly involving muscles, tendons and bones and the nervous system. This includes a recommendation to not use them for mild or moderately severe infections unless other antibiotics cannot be used.
- 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, co-trimoxazole, October 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 because 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 receiving treatment 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 USA 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, sputum colour changes). 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 received treatment in the community, about 14 people would need antibiotics to prevent 1 person from having treatment failure (no improvement in symptoms). In people who received treatment in hospital, about 10 people would need 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 subgroup 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, there was uncertain evidence about which groups of people may benefit most from antibiotics, although the committee noted that the NNT for symptoms that didn't resolve or improve was 3 in people receiving treatment in intensive care.
- The committee agreed that the limited benefit was likely to be because many acute exacerbations are not caused by bacterial infections, but may be caused by viral infections or environmental factors, such as smoking.

Rationale for decision-making

- No evidence was identified on back-up antibiotics and the committee was not able to make a recommendation for people with an acute exacerbation of COPD.
- The committee acknowledged the recommendations in the NICE guideline on COPD in over 16s, which cover managing acute exacerbations, including self-management. They recognised that some people at risk of exacerbations may have antibiotics to keep at home as part of their exacerbation action plan. 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 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. They were concerned that repeated use of antibiotics means that they will not continue to be effective in the future.
- The committee agreed that the evidence suggested that antibiotics had some clinical benefit in a heterogeneous population with acute exacerbations of COPD, in the context of increased harms with antibiotics and antimicrobial resistance. The committee recognised that there isn't a clear distinction between severity of exacerbation and presence of a bacterial infection.
- From the evidence identified, the committee agreed that it was not possible to identify which people with an acute exacerbation are more likely to benefit from antibiotics. However, from their experience, and based on existing expert consensus, the presence of sputum colour changes and increases in volume or thickness beyond the person's normal day-to-day variation appear to be important factors.
- From experience, the evidence identified and the need to minimise the risk of antimicrobial resistance, the committee agreed that an antibiotic for an acute exacerbation of COPD should be considered on an individual patient basis. This should take into account the uncertain benefit of antibiotics, increased risk of harms and the risk of antimicrobial resistance with repeated courses, balanced against severity of their symptoms (particularly sputum colour changes and increases in volume or thickness beyond the person's normal day-to-day variation), their need for hospital treatment, their exacerbation and hospitalisation history, their risk of complications, and previous sputum culture results.
- From experience, the committee recognised that a person's condition may change rapidly during an acute exacerbation. They 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 within 2 to 3 days (or other agreed time), or they become systemically very unwell.

- The committee was aware of recommendations from the NICE guideline on COPD in over 16s and NICE guideline on 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, fluoroquinolones 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 who received treatment 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 receiving treatment 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 receiving treatment in the community.
- Dimopoulos et al. (2007) included 4 RCTs in people receiving treatment in the community and 6 RCTs in people receiving treatment in hospital (4 of these RCTs had a mixed population who received treatment in the community or in hospital).
- The diagnosis of an acute exacerbation and the type of symptoms was based on the Anthonisen classification of type of exacerbation. 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, fluoroquinolones, cephalosporins and trimethoprim (with or without a sulfonamide) 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 fluoroquinolones) for 3 to 10 days found no significant difference in clinical effectiveness between groups (moderate to high quality evidence). Most people included in this review received treatment 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).

- 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 fluoroquinolones (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 a day for 10 days was compared with ciprofloxacin 750 mg twice a day 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 fluoroquinolones (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 in over 16s makes recommendations about when to send sputum for culture.
- 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 because 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 (a macrolide), used at the usual doses for an acute exacerbation of COPD, although the dosage may be increased in severe infections. These antibiotics have good activity against common pathogens, such as Streptococcus pneumoniae and Haemophilus influenzae. Where a person is

receiving prophylactic antibiotics, antibiotic treatment for an acute exacerbation 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 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 may be at a higher risk of treatment failure (for example, people who have had repeated courses of antibiotics, previous or current sputum culture with resistant bacteria, or people at higher risk of developing complications).
- The alternative oral antibiotics for people who may be at a higher risk of treatment failure (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
  - **levofloxacin** 500 mg once a day; which was a fluoroquinolone used in the studies
  - **co-trimoxazole** 960 mg twice a day (trimethoprim plus a sulfonamide); which is suitable only for people with bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic.
- The committee was aware of the EMA's Pharmacovigilance Risk Assessment Committee recommendation to restrict the use of fluoroquinolone antibiotics following a review of disabling and potentially long-lasting side effects mainly involving muscles, tendons and bones and the nervous system. However, they discussed that fluoroquinolones are appropriate as an alternative option for people who may be at a higher risk of treatment failure. The committee was keen to point out, however, that fluoroquinolone safety concerns should be taken into account on an individual patient basis.
- First-choice intravenous antibiotics at usual doses for treating acute exacerbations in people who are unable to take oral antibiotics, or the severity of their exacerbation means than intravenous treatment is required, are:

  - **amoxicillin**
  - **co-amoxiclav**
  - **clarithromycin**
  - **co-trimoxazole**
  - **piperacillin with tazobactam** (an antipseudomonal penicillin with a beta-lactamase inhibitor).

- 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 their symptoms 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 to 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 fluoroquinolones 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 discussion 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.
- In line with the NICE guideline on antimicrobial stewardship and Public Health England's 'Start smart – then focus' toolkit, 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.

See the full evidence review for more information.

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 the Drug Tariff for costs.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on antimicrobial stewardship.

For full details of the evidence and the guideline committee's discussion, see the evidence review. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put this guidance into practice.

Update information

Minor changes since publication

September 2019: Minor wording changes were made and footnotes were updated in table 1 to reflect new restrictions and precautions for the use of fluoroquinolone antibiotics.

June 2019: Information on dosage of clarithromycin for severe infections was amended.

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