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Guidelines for the management of adult lower respiratory tract infections - Summary

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Abstract

This document is an update of Guidelines published in 2005 and now includes scientific publications through to May 2010. It provides evidence-based recommendations for the most common management questions occurring in routine clinical practice in the management of adult patients with LRTI. Topics include management outside hospital, management inside hospital (including community-acquired pneumonia (CAP), acute exacerbations of COPD (AECOPD), acute exacerbations of bronchiectasis) and prevention. The target audience for the Guideline is thus all those whose routine practice includes the management of adult LRTI.

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Introduction

In 2005 the European Respiratory Society (ERS), in collaboration with The European Society for Clinical Microbiology and Infectious Diseases (ESCMID), published guidelines on the management of lower respiratory tract infections (LRTIs) in adults [1]. This document was based on published scientific literature up to the end of 2002. We have now updated these guidelines to include publications to May 2010. The taskforce responsible for guideline development has been sponsored by the ERS and ESCMID. Members of the taskforce are members of the sponsoring ERS and/or ESCMID.

Our objective is to provide evidence-based recommendations for the most common management questions occurring in routine clinical practice in the management of adult patients with LRTI. The target audience for the guidelines is thus all those whose routine practice includes the management of adult LRTI.

This short document covers only the statements and recommendations in the guidelines. A much more detailed document, including not only the recommendations but also background information for each recommendation with

details about each new cited reference and the evidence grades, is available on the ERS and ESCMID websites. Both documents are divided into background information about microbial causes, antibiotic resistance and pharmacodynamics, and then the guideline section, which captures management outside hospital, management inside hospital (including community-acquired pneumonia (CAP), acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and acute exacerbations of bronchiectasis) and prevention. The guidelines are about the management of infection. This means that for conditions such as AECOPD, aspects of management that are unrelated to infection (e.g. use of steroids or bronchodilators) are not included.

Because this is an update, original data and publications have usually not been repeated and the reader is referred to the original publication [1] for this.

Methods

Using the same search filter as for the 2005 document (this is described in detail in the previous publication [1] and website documents—http://www.ersnet.org; http://www.escmid.org) we identified relevant manuscripts in PubMed published from July 2002 to May 2010. We retrieved 15 261 titles and loaded them into an electronic database. From these, 1677 titles were identified as potentially relevant publications by the expert panel members. The same process of evidence appraisal and grading and recommendation development and grading as in the 2005 document was used. As this is an update using the same methodologies, the layout of the document, including text, recommendations and evidence tables, is the same as 2005.

The document takes each clinical question for which there was a recommendation in the 2005 guideline and presents new information when available followed by a new recommendation. In some circumstances, because of lack of new evidence, or sometimes even in the presence of new evidence, the recommendation is unchanged from 2005. Where this is the case it is indicated.

In some parts of the guidelines new questions and recommendations have been added to cover relevant areas not included in the 2005 guidelines (e.g. aspiration pneumonia).

LRTI Definitions

The guidelines are to be used to guide the management of adults with lower respiratory tract infection (LRTI). As will be seen in the following text, this diagnosis, and the other clinical syndromes within this grouping, can be difficult to make accurately. In the absence of agreed definitions of these syndromes these guidelines are to be used when, in the opinion of a clinician, an LRTI syndrome is present. The following are put forward as definitions to guide the clinician, but it will be seen in the ensuing text that some of these labels will always be inaccurate. These definitions are pragmatic and based on a synthesis of available studies. They are primarily meant to be simple to apply in clinical practice, and this might be at the expense of scientific accuracy. These definitions are not mutually exclusive, with lower respiratory tract infection being an umbrella term that includes all others, which can also be used for cases that cannot be classified into one of the other groups. No new evidence has been identified that would lead to a change in the clinical definitions, which are therefore unchanged from the 2005 publication.

Since the publication of the 2005 guidelines the term health care-associated pneumonia (HCAP) has been put forward to capture groups of patients with pneumonia, some acquired outside hospital, expected to be caused by similar pathogens, but different from those usually found in community-acquired LRTI. In the opinion of the taskforce members the evidence base does not support the use of this term as being clinically relevant in Europe at the present time. HCAP is therefore not covered further in this document [2–17].

Lower respiratory tract infection

An acute illness (present for 21 days or less), usually with cough as the main symptom, with at least one other lower respiratory tract symptom (sputum production, dyspnoea, wheeze or chest discomfort/pain) and no alternative explanation (e.g. sinusitis or asthma).

Acute bronchitis (AB)

An acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI, and no alternative explanation (e.g. sinusitis or asthma).

Influenza

An acute illness, usually with fever, together with the presence of one or more of headache, myalgia, cough and sore throat.

Suspected community-acquired pneumonia (CAP)

An acute illness with cough and at least one of new focal chest signs, fever >4 days or dyspnoea/tachypnoea, and without other obvious cause.

Definite community-acquired pneumonia (CAP)

As above but supported by chest radiograph findings of lung shadowing that is likely to be new. In the elderly, the

presence of chest radiograph shadowing accompanied by acute clinical illness (unspecified) without other obvious cause.

Acute exacerbation of COPD (AECOPD)

An event in the natural course of the disease characterized by a worsening of the patient's baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management. If chest radiograph shadowing, consistent with infection, is present the patient is considered to have CAP.

Acute exacerbation of bronchiectasis (AEBX)

In a patient with features that suggest bronchiectasis, an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea and/or cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management. If chest radiograph shadowing, consistent with infection, is present the patient is considered to have CAP.

Background

What new information is available about the microbiological causes of LRTI?

There has been no major change in causative pathogens for LRTI. More information is available about the frequency of polymicrobial infections, including viral infections. PVL-producing *Staphylococcus aureus* has emerged as a new cause, often of severe CAP, but currently remains uncommon [18–90].

What information is available about the frequency and clinical relevance of antimicrobial resistance in these settings?

1 In pneumococci, erythromycin MICs >0.5 mg/L predict clinical failure. The prevalence of resistance (R) in many countries compromises the efficacy of macrolides in the treatment of pneumococcal infection. The prevalence of resistance will dictate the need to reassess current recommendations for the treatment of CAP.
2 Adequate choice and dosing of selected β-lactams is still useful in the treatment of extrameningeal pneumococcal infections. No documented failures in patients with extrameningeal infections due to penicillin R strains treated with adequate doses of penicillins and third generation cephalosporins. Penicillin, 2 g (3.2 mU) i.v. Q 4 h, should be adequate for strains with a penicillin MIC of ≤8 mg/L; adjust dose for renal impairment; ceftriaxone 1 g i.v. or i.m. Q 12 h or cefotaxime 2 g i.v. Q 6 h, should be adequate for strains with n MIC of ≤8 mg/L. New formulation of amoxicillin/clavulanate (2 g/125 Q 12 h) eradicated amoxicillin-resistant strains (MICs, 4–8 mg/L) in two randomized controlled trials. Oral cephalosporins are not adequate for the treatment of infection caused by strains with penicillin MICs >2 mg/L.
3 Fluoroquinolones are highly active and efficacious against respiratory pathogens; they should be used in well-defined circumstances. If the prevalence of first step mutants is low, the use of the most potent FQ is a logical choice if resistance has to be avoided/delayed. Previous exposure to an FQ in the recent past precludes the use of a member of this class for the empirical treatment of CAP.
4 Macrolides show, at best, only modest activity against *H. influenzae*. The existence of efflux pumps leads to loss of susceptibility to this class in more than 98% of *H. influenzae* strains.
5 Among 'atypicals', antibiotic resistance is rare and very seldom responsible for clinical failures.
6 Macrolide resistance in *Mycoplasma pneumoniae* is rising in Japan; there is a need for European local surveillance studies.
7 The role of community-acquired meticillin-resistant *Staphylococcus aures* (CA-MRSA) in CAP is poorly defined, although emergent in Europe. CA-MRSA is usually only resistant to the β-lactams and susceptible to most other antibiotic classes. The antibiotic treatment of CA-MRSA pneumonia is not known. As suppression of toxin production may correlate with improved outcome, vancomycin alone may not be the optimal treatment for pneumonia. Thus, the combination of a bactericidal agent with a toxin-suppressing agent, such as clindamycin or linezolid, has been suggested as the optimal choice.
8 The *in vivo* selection of resistance that results from inappropriate antimicrobial therapy is a warning that emphasizes the importance of the proper use of antimicrobials [91–128].

What new information is available about antimicrobial pharmacokinetics and pharmacodynamics?

The only new information is about the need for high levofloxacin doses (750 mg once daily) in the treatment of *Pseudomonas* and *Klebsiella* [129,130]. Two other new studies do now alter the current guideline recommendations [131,132].

Management Outside Hospital

Introduction

Lower respiratory tract infection is a broad description of a group of disease entities, encompassing acute bronchitis, pneumonia and exacerbations of chronic lung disease. In primary

care it is very difficult to differentiate between those different diseases without doing extensive additional diagnostic tests. Patients can present with cough, dyspnoea, tachypnoea, fever, pain in the chest, wheezing and auscultatory abnormalities. There is huge overlap in presentation between the different lower respiratory diseases mentioned above and it is neither feasible nor cost-efficient to do a full diagnostic work-up in all patients. Therefore an empirical and pragmatic approach is warranted. The statements and recommendations below are based on primary care studies, expert opinion and consensus among members of the working group.

Diagnosis

When should aspiration pneumonia be considered? 'Aspiration pneumonia should be considered in patients with difficulties with swallowing who show signs of an acute LRTI. In these patients a chest X-ray should be performed' [C3].

No new information. Recommendation not changed.

When should left ventricular failure be considered? 'Left ventricular failure should be considered in patients above 65, with either orthopnoea, displaced apex beat and/or a history of myocardial infarction, hypertension or atrial fibrillation'.

'Low serum levels of Atrial Natriuretic Peptide (BNP <40 pg/mL) or NT pro-BNP <150 pg/mg) make the presence of left ventricular failure unlikely' [C3].

New information. Recommendation not changed [133–135].

When should pulmonary embolism be considered? 'Pulmonary embolism should be considered in patients with one of the following characteristics: a history of DVT or pulmonary embolism, immobilization in the past 4 weeks, or malignant disease' [C3].

No new information. Recommendation not changed.

When should chronic airway disease be considered? 'In patients with a persistent cough and at least two of the following, wheezing (either as sign or as symptom), previous consultations for wheezing or cough, dyspnoea, prolonged expiration, a smoking history and symptoms of allergy, lung-function tests should be considered to assess the presence of chronic airway disease. In elderly patients who smoke and present with a cough, COPD should be considered' [B1] [136,137].

How to differentiate between pneumonia and other respiratory tract infections. 'A patient should be suspected of having pneumonia when one of the following signs and symptoms are present: new focal chest signs, dyspnoea, tachypnoea, pulse rate >100 or fever >4 days. In patients with a suspected pneumonia a test for serum-level of C-reactive protein (CRP) can be done. A level of CRP <20 mg/L at presentation, with symptoms for >24 h, makes the presence of pneumonia highly unlikely; a level of >100 mg/L makes pneumonia likely'.

'In case of persisting doubt after CRP testing, a chest X-ray should be considered to confirm or reject the diagnosis' [B1] [138–143].

Should the primary care physician test for a possible microbiological aetiology of LRTI? 'Microbiological tests such as cultures and gram stains are not recommended' [B1].

'Biomarkers to assess the presence of a bacterial pathogen are not recommended in primary care' [A1] [141,142,144].

New information. Recommendation not changed.

Prognosis

How should the risk of complications be assessed in a primary care patient with LRTI? 'Patients with an elevated risk of complications should be monitored carefully and referral should be considered. In patients over 65 years of age the following characteristics are associated with a complicated course: presence of COPD, diabetes or heart failure, previous hospitalization in the past year, taking oral glucosteroids, antibiotic use in the previous month, general malaise, absence of upper respiratory symptoms, confusion/diminished consciousness, pulse >100, temperature >38, respiratory rate >30, blood pressure <90/60, and when the primary care physician diagnoses pneumonia [A3]. In patients under 65 the working group thinks that diabetes, a diagnosis of pneumonia and possibly also asthma are risk factors for complications. For all age groups, serious conditions such as active malignant disease, liver and renal disease and other disorders that are relatively rare in primary care but affect immunocompetence, do also increase risk of complications' [C3] [145–150].

Treatment

Should symptomatic acute cough be treated? 'Cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute LRTI in primary care' [A1] [151–153].

When should antibiotic treatment be considered in patients with LRTI? Antibiotic treatment should be prescribed in patients with suspected or definite pneumonia (see How to differentiate between pneumonia and other respiratory tract infections) [C1].

Antibiotic treatment should be considered for patients with LRTI and serious comorbidity such as:

1 selected exacerbations of COPD; (see below)
2 cardiac failure;
3 insulin-dependent diabetes mellitus;
4 a serious neurological disorder (stroke etc.) [C3] [154,155].

What are the indications for antibiotic treatment of acute exacerbations of chronic obstructive lung disease (COPD)? 'An antibiotic should be given in exacerbations of COPD in patients with all three of the following symptoms: increased dyspnoea, sputum volume and sputum purulence. In addition, antibiotics should be considered for exacerbations in patients with severe COPD' [C1].

New information. Recommendation not changed [156].

Which antibiotics should be used in patients with LRTI? 'Amoxicillin or tetracycline should be used as the antibiotic of first choice based on least chance of harm and wide experience in clinical practice. In the case of hypersensitivity, a tetracycline or macrolide such as azithromycin, clarithromycin, erythromycin or roxithromycin is a good alternative in countries with low pneumococcal macrolide resistance. National/local resistance rates should be considered when choosing a particular antibiotic. When there are clinically relevant bacterial resistance rates against all first choice agents, treatment with levofloxacin or moxifloxacin may be considered' [C1] [157,158].

Is antiviral treatment useful in patients with LRTI? 'The empirical use of antiviral treatment in patients suspected of having influenza is usually not recommended [B1]. Only in high-risk patients who have typical influenza symptoms (fever, muscle ache, general malaise and respiratory tract infection), for <2 days and during a known influenza epidemic, can antiviral treatment can be considered' [A1].

New information. Recommendation not changed [159,160].

How should patients with LRTI be monitored? 'A patient should be advised to return if the symptoms take longer than 3 weeks to disappear'.

'Clinical effect of antibiotic treatment should be expected within 3 days and patients should be instructed to contact their doctor if this effect is not noticeable. Seriously ill patients, meaning those with suspected pneumonia and elderly with relevant co-morbidity, should be followed-up 2 days after the first visit'.

'All patients or persons in their environment should be advised to contact their doctor again if fever exceeds 4 days, dyspnoea gets worse, patients stop drinking or consciousness is decreasing' [C3].

No new information. Recommendation rephrased.

When should patients with LRTI be referred to hospital? In the following categories of patients, referral to hospital should be considered.

1 Severely ill patients with suspected pneumonia (the following signs and symptoms are especially relevant here: tachypnoea, tachycardia, hypotension and confusion).
2 Patients with pneumonia who fail to respond to antibiotic treatment.
3 Elderly patients with pneumonia and elevated risk of complications, notably those with relevant co-morbidity (diabetes, heart failure, moderate and severe COPD, liver disease, renal disease or malignant disease).
4 Patients suspected of pulmonary embolism.
5 Patients suspected of malignant disease of the lung [C3].

These recommendations are based on consensus in the working group. There are no studies comparing different referral strategies.

Management Inside Hospital

Community-acquired pneumonia

Who should be admitted to hospital? 'The decision to hospitalize remains a clinical decision. However, this decision should be validated against an objective tool of risk assessment. The CRB-65 is most practical in its simplicity. In patients meeting a CRB-65 of one or more (except age ≥65 as the only criterion met), hospitalization should be seriously considered [A3]. Biomarkers (e.g. CRP or procalcitonin) have a significant potential to improve severity assessment but have not been sufficiently evaluated for the decision to hospitalize. [A3] [141,145,161–191].

Who should be considered for ICU admission? 'Findings reflecting acute respiratory failure, severe sepsis or septic shock and radiographic extension of infiltrates, as well as severely decompensated comorbities, should prompt consideration of admission to the ICU or an intermediate care unit' [A3].

'The predictive potential of rules for the prediction of ICU admission depends on local facilities. Therefore, it appears that severity criteria should be used to indicate the need for intensive care treatment rather than care in a special unit'.

'The presence of at least two of systolic blood pressure <90 mmHg, severe respiratory failure (PaO_2/F_IO_2 <250) or involvement of >2 lobes on chest radiograph (multilobar involvement), or one of requirement for mechanical ventilation or requirement for vasopressors >4 h (septic shock),

indicates severe CAP. Alternatively, the presence of several minor criteria as provided in the last IDSA/ATS update may indicate severe CAP.' [A3].

'Both rules should increase the attention given to the recognition of patients with unstable courses of pneumonia in order to avoid delayed transfer to the ICU' [192–200].

What is the value of blood cultures in the diagnosis of community-acquired pneumonia? 'Two sets of blood cultures should be performed in all patients with CAP who require hospitalization' [A3].

New information. Recommendation not changed [61,201–205].

What other invasive techniques for normally sterile specimens can be useful in the laboratory diagnosis of pneumonia? (a) *Thoracentesis*: diagnostic thoracentesis should be performed in hospitalized patients with CAP when a significant (as judged by the admitting physician) pleural effusion is present [A3].

No new information. Recommendation not changed.

(b) *Transthoracic needle aspiration (TNA)*: because of the inherent potential adverse effects, TNA can be considered ONLY on an individual basis for some severely ill patients, with a focal infiltrate, in whom less invasive measures have been non-diagnostic [A3].

No new information. Recommendation not changed.

(c) *Bronchoscopic protected specimen brush (PSB) and bronchoalveolar lavage (BAL) and quantitative endotracheal aspirates (QEA)*: BAL should be the preferred technique in non-resolving pneumonia [A3].

'Bronchoscopic sampling of the lower respiratory tract can be considered in intubated patients and selected non-intubated patients, where gas exchange status allows' [A3].

New information. Recommendation not changed [206].

What is the value of sputum examination? Gram strain: should be performed when a purulent sputum sample can be obtained from patients with CAP and processed in a timely manner. The presence of a predominant bacterial morphotype allows inference of the aetiological bacterial species and interpretation of the results of sputum culture [A3].

New information. Recommendation not changed [207–213].

Culture: a culture from a purulent sputum specimen of a bacterial species compatible with the morphotype observed in the Gram stain, which is processed correctly, should be considered for confirmation of the species identification and antibiotic susceptibility testing [B3].

No new information. Recommendation not changed.

What can antigen tests offer in the diagnosis of community acquired pneumonia? 'The immunochromatographic urinary antigen test for *S. pneumoniae* should be performed in patients admitted to the hospital for reasons of illness severity. This test should also be considered whenever a pleural fluid sample is obtained in the setting of a parapneumonic effusion' [A3].

'Urine *L. pneumophila* serogroup 1 antigen detection should be performed in patients admitted to the hospital for reasons of severity and in other patients where this infection is clinically or epidemiologically suspected [A3]. *L. pneumophila* serogroup 1 antigen detection in urine is the most rapid method to diagnose or exclude the infection. A negative test makes legionella unlikely, but does not exclude legionella infection' [A3] [209,214–242].

What can serological tests offer in the diagnosis of pneumonia? 'Serology for infections caused by *M. pneumoniae*, *C. pneumoniae* and *Legionella* is more useful in epidemiological studies than in the routine management of the individual patient. If aetiological diagnosis of the atypical agents is considered in the management of the individual patient (e.g. in patients not responding to β-lactam therapy), serological tests should not be performed as the only routine diagnostic test [A3]. A combination of IgM antibody detection and PCR may be the most sensitive approach' [A3] [243–250].

Are amplification tests useful for the diagnosis of LRTI? Where available, application of quantitative molecular tests for the detection of *Streptococcus pneumoniae*, both in sputum and in blood, may be valuable in CAP patients in whom antibiotic therapy has been initiated and may be a useful tool for severity assessment. Application of molecular tests for the detection of influenza and respiratory syncytial virus should be considered during the winter season and for the detection of atypical pathogens provided the tests are validated and the results can be obtained sufficiently rapidly to be therapeutically relevant' [A3] [18,246–249,251–266].

What classification should be used for treatment? 'Antimicrobial treatment has to be empirical and should follow an approach according to the individual risk of mortality. The assessment of severity according to mild, moderate and severe pneumonia implies a decision about the most appropriate treatment setting (ambulatory, hospital ward or ICU) [A4]. Antimicrobial treatment should be initiated as soon as possible [A3]'.

When should antibiotics be administered after diagnosis of pneumonia? 'Antibiotic treatment should be initiated immediately after diagnosis of CAP [C3]. In patients with CAP and septic

shock, delay must not be more than 1 h after diagnosis [A1]' [267–273].

What initial empirical treatments are recommended? Treatment options for hospitalized patients with community-acquired pneumonia (no need for intensive care treatment) (in alphabetical order) [C4].

Aminopenicillin ± macrolide[a,b]
Aminopenicillin/β-lactamase inhibitor[a] ± macrolide[b]
Non-antipseudomonal cephalosporin
Cefotaxime or ceftriaxone ± macrolide[b]
Levofloxacin[a]
Moxifloxacin[a,c]
Penicillin G ± macrolide

[a]Can be applied as sequential treatment using the same drug.
[b]New macrolides preferred to erythromycin.
[c]Within the fluoroquinolones, moxifloxacin has the highest antipneumococcal activity.
[d]In patients at risk of gram-negative enteric bacterium, particularly strains with extended-spectrum β-lactamase, but without risk (or after exclusion) of *P. aeruginosa*, ertapenem may be used [100,158,274–304].

Treatment options for patients with severe community-acquired pneumonia [C4] (ICU or intermediate care).

No risk factors for *P. aeruginosa*
Non-antipseudomonal cephalosporin III + macrolide[a]
or
moxifloxacin or levofloxacin ± non-antipseudomonal cephalosporin III
Risk factors for *P. aeruginosa*
Antipseudomonal cephalosporin[b] or acylureidopenicillin/β-lactamaseinhibitor or carbapenem (meropenem preferred, up to 6 g possible, 3 × 2 in 3-h infusion)
PLUS
ciprofloxacin[c] OR
PLUS
macrolide[a] + aminoglycoside (gentamicin, tobramycin or amikacin)

[a]New macrolides preferred to erythromycin.
[b]Ceftazidime has to be combined with penicillin G for coverage of *S. pneumoniae*.
[c]Levofloxacin 750 mg/24 h or 500 mg twice daily is an alternative and also covers Gram-positive bacteria if treatment is empirical [301,305–315].

What is the recommended treatment for specific identified pathogens?

Pathogen	Recommended treatment
Highly resistant *S. pneumoniae* (>8 mg/dL)	Levofloxacin Moxifloxacin Vancomycin, teicoplanin Linezolid
MSSA	Flucloxacillin Cephalosporin II Clindamycin Levofloxacin Moxifloxacin
MRSA	Vancomycin, teicoplanin ± rifampin Linezolid (Clindamycin if sensitive)
Ampicillin-resistant *H. influenzae*	Aminopenicillin plus β-lactamase inhibitor Levofloxacin Moxifloxacin
Mycoplasma pneumoniae	Doxycycline Macrolide Levofloxacin Moxifloxacin
Chlamydophila pneumoniae	Doxycycline Macrolide Levofloxacin Moxifloxacin
Legionella spp.	Levofloxacin Moxifloxacin (most data available for levofloxacin) Macrolide (azithromycin preferred) ± Rifampicin
Coxiella burnetii	Doxycycline Levofloxacin Moxifloxacin
Acinetobacter baumanii	Third-generation cephalosporin + aminoglycoside Ampicillin-sulbactam

No experience in pneumonia for tigecycline [99,316–322].

What should be the duration of treatment? The duration of treatment should generally not exceed 8 days in a responding patient [C2]. Biomarkers, particularly PCT, may guide shorter treatment duration [323–331].

When should intravenous treatment be used and when should the switch to oral occur? In ambulatory pneumonia, treatment can be applied orally from the beginning [A3]. Some carefully selected hospital inpatients may also be candidates for exclusively oral treatment.

'In hospitalized patients, sequential treatment should be considered in all patients except the most severely ill. The optimal time to switch to oral treatment is also unknown; this decision should be guided by the resolution of the most prominent clinical features at admission [A3]. In most patients it is probably not necessary to observe patients in hospital after having switched to oral treatment [A3]. Switch to oral treatment after reaching clinical stability is also safe in patients with severe pneumonia' [A2] [332–338].

Which additional therapies are recommended? 'All patients should be subject to early mobilization' [A3].

'Low molecular weight heparin should be given in patients with acute respiratory failure [A3]. The use of non-invasive ventilation is not yet standard care but can be considered, particularly in patients with COPD [B3] and ARDS' [A3].

'The treatment of severe sepsis and septic shock is confined to supportive measures' [A3].

'Steroids are not recommended in the treatment of pneumonia [339–347]' [A3].

When should aspiration pneumonia be suspected? There is no agreed definition. Aspiration pneumonia should be suspected in those with CAP which either:

1 follows an episode of witnessed aspiration; or
2 occurs in the presence of risk factors for aspiration, including reduced consciousness level, and dysphagia due to mechanical or neurological upper digestive tract dysfunction [C3] [6,44,348–355].

Evidence Table

What empirical antibiotic treatment is recommended for aspiration pneumonia?

Hospital ward, admitted from home	ICU or admitted from nursing home
Oral or i.v. β-lactam/β-lactamase inhibitor or Clindamycin or i.v. cephalosporin + oral metronidazole or moxifloxacin	Clindamycin + cephalosporin or Cephalosporin + metronidazole

Refs. [6,44,351,352,356–361].

How should response be assessed and when should chest radiograph be repeated? 'Response to treatment should be monitored by simple clinical criteria, including body temperature, respiratory and haemodynamic parameters. The same parameters should be applied to judge suitability for hospital discharge [A3]. Complete response, including radiographical resolution, requires longer time periods. C-reactive protein should be measured on days one and three/four, especially in those with unfavourable clinical parameters. The same clinical parameters should be applied to judge suitability for hospital discharge [A3]. Discharge decisions should be based on robust markers of clinical stabilization [A3]' [176,199,362–365].

How should the non-responding patient be assessed? 'Two types of treatment failures, non-responding pneumonia and slowly resolving pneumonia, should be differentiated [A3]. Non-responding pneumonia occurring in the first 72 h of admission is usually due to antimicrobial resistance or an unusually virulent organism or a host defence defect or wrong diagnosis. Non-response after 72 h is usually due to a complication. The evaluation of non-responding pneumonia depends on the clinical condition. There are no trials of different approaches to the non-responding patient to guide this recommendation. In unstable patients, full reinvestigation followed by a second empirical antimicrobial treatment regimen should be carried out. The latter may be withheld in stable patients. Slowly resolving pneumonia should be reinvestigated according to clinical needs, the condition of the patient and his individual risk factors [C3]'.

Exacerbations of chronic obstructive pulmonary disease

Which hospitalized patients with COPD exacerbations should receive antibiotics?

1 Patients with all three of the following symptoms: increased dyspnoea, sputum volume and sputum purulence (a type I Anthonisen exacerbation) [A2].
2 Patients with only two of the above three symptoms (a type II Anthonisen exacerbation) when increased purulence of sputum is one of the two cardinal symptoms [A2].
3 Patients with a severe exacerbation that requires invasive or non-invasive mechanical ventilation [A2].
4 Antibiotics are generally not recommended in Anthonisen type II without purulence and type III patients (one or less of the above symptoms) [A2].

New information. Recommendation not changed [366–373].

What stratification of patients with COPD exacerbation is recommended to direct treatment? *Group A*: admitted to hospital without risk factors for *P. aeruginosa* infection [A3].

Group B: admitted to hospital with risk factors for *P. aeruginosa* [A3].

New information. Recommendation reworded, but not changed [374–378].

What are the risk factors for P. aeruginosa? *P. aeruginosa* should be considered in the presence of at least two of the following.

1 Recent hospitalization [A3].
2 Frequent (>4 courses per year) or recent administration of antibiotics (last 3 months) [A3].
3 Severe disease (FEV1 <30%) [A3].
4 Oral steroid use (>10 mg of prednisolone daily in the last 2 weeks) [A3] [83,379–381].

Which microbiological investigations are recommended for the hospitalized patient with COPD exacerbation? 'Sputum cultures or endotracheal aspirates (in mechanically ventilated patients) should be obtained and are a good alternative to bronchoscopic procedures for evaluation of the bacterial burden by potential pathogenic microorganisms' [A3].

Recommendation modified [84,367,382–388].

Which initial antimicrobial treatments are recommended for patients admitted to hospital with COPD exacerbation?

1 In patients without risk factors for *P. aeruginosa* several options for antibiotic treatment are available. The

selection of one or other antibiotic should depend on the severity of the exacerbation, local pattern of resistances, tolerability, cost and potential compliance. Co-amoxiclav is recommended while levofloxacin and moxifloxacin are alternatives [A2].

2 In patients with risk factors for *P. aeruginosa*, ciprofloxacin (or levofloxacin 750 mg/24 h or 500 mg twice daily) is the antibiotic of choice when the oral route is available. When parenteral treatment is needed, ciprofloxacin or a β-lactam with antipseudomonal activity are the options available. The addition of aminoglycosides is optional [A2].
3 The use of the oral or intravenous route should be guided by the stability of the clinical condition and the severity of exacerbation. Switch (intravenous to oral) should be done by day three of admission if the patient is clinically stable [A3] [389–391].

How should the non-responding patient with COPD exacerbation be assessed?

1 After close re-evaluation of non-infectious causes of failure (i.e. inadequate medical treatment, embolisms, cardiac failure, other) a careful microbiological reassessment, as mentioned in the section on microbiological diagnosis, should be considered [C3].

2 Change to an antibiotic with good coverage against *P. aeruginosa*, *S. pneumoniae* resistant to antibiotics and non-fermenters, and subsequent adjustment of the new antibiotic treatment according to microbiological results, should be considered for treatment in cases of failure [C3].

New information. Recommendation not changed [392].

Exacerbations of bronchiectasis

General recommendations for exacerbations of bronchiectasis.

1 Periodic surveillance of colonization should be considered [B3].
2 Antibiotic treatment should be given to patients with exacerbations [B3].
3 Obtaining a sputum sample for culture before starting antibiotic treatment should be done in most cases and particularly in those requiring hospitalization [B3].
4 For empirical antibiotic treatment, patients should be stratified according to the potential risk of *Pseudomonas* spp infection [B3] (see What are the risk factors for *P. aeruginosa*, above). Recommended antibiotics are summarized in the box below.
5 Empirical antibiotics should be adjusted or modified according to sputum culture results [A3].

New information. Recommendation not changed [393,394].

What antibiotics are recommended for exacerbations of bronchiectasis? [C4].

	Oral treatment	Parenteral treatment
No risk of Pseudomonas spp	Amoxicillin-clavulanate Moxifloxacin Levofloxacin	
Risk of Pseudomonas spp[a]	Ciprofloxacin[b]	Ceftazidime or carbapenem or piperacillin-tazobactam

[a]Use the same criteria mentioned for chronic obstructive pulmonary disease exacerbation.
[b]Levofloxacin 750 mg/24 h or 500 mg twice daily is an alternative.
Refs. [88, 393,394].

Prevention

Prevention by methods other than vaccination

Does oral immunization with bacterial extracts prevent LRTI? In patients with chronic bronchitis (CB) or COPD, *H. influenzae* oral vaccine [B1] or bacterial extracts (OM-85 BV) [B2] should not be given.

New information. Recommendation not changed [395–398].

What is the role of prophylactic antibiotic therapy in chronic bronchitis or COPD? In patients with CB or COPD, oral or parenteral antibiotics should not be given for prevention [A1].

New information. Recommendation not changed [399–401].

What is the role of prophylactic antibiotic therapy in patients with COPD or bronchiectasis? (a) *COPD*: the use of nebulized antibiotics or intermittent long-term macrolide therapy is not recommended in COPD patients in general [C4] [402].

(b) *Bronchiectasis—nebulized antibiotics*: there is not enough evidence to recommend the use of nebulized antibiotics (tobramycin) in non-cystic fibrosis-bronchiectasis [C2] [403,404].

(c) *Bronchiectasis—macrolides*: there is not enough evidence to recommend the use of intermittent long-term macrolide therapy in non-cystic fibrosis-bronchiectasis in general [C2] [405,406].

Does antibiotic treatment of upper respiratory tract infections prevent LRTI? 'Antibiotics should not be given as treatment for URTI to prevent LRTI' [A1].

No new information. Recommendation not changed.

Does treatment with inhaled steroids or long-acting beta-2-agonists or long-acting anti-muscarinics prevent LRTI? Inhaled steroids [B1] or long-acting beta-2-agonists [C4] or long-acting anti-muscarinics [C4] should not be used to prevent LRTI (this does not mean that they might not prevent exacerbations of COPD, which is an issue beyond the scope of this document).

No new information. Recommendation not changed.

Does regular physiotherapy prevent LRTI? Physiotherapy should not be used as a preventive approach against LRTI [C4].

No new information. Recommendation not changed.

Do antiviral substances prevent influenza virus infection? Prevention of influenza by antiviral substances should only be considered in special situations (for example in outbreaks in closed communities during influenza seasons) [A1]. In the case of seasonal influenza outbreaks or a pandemic situation the national recommendations should be followed.

New information. Recommendation not changed [407].

Are oral mucolytics useful for the prevention of LRTI? In patients with bronchiectasis, oral mucolytics should not be used for prevention of LRTI [B1]. Prescription of oral mucolytics through the winter months should be considered for those who have frequent or prolonged exacerbations, or those who are repeatedly admitted to hospital with exacerbations of COPD and for whom inhaled corticosteroids (ICS) are not prescribed [B1] [408].

Is there evidence that homeopathic substances prevent LRTI? Homeopathic substances should not be used as a preventive measure against LRTI [C4].

New information Recommendation not changed [409–411].

Oral care in nursing homes. Intensified oral care in nursing home residents should be considered as a preventive measure to reduce the incidence of pneumonia and the risk of death from pneumonia in these patients [B1] [412–414].

Are there commonly used medications decreasing the risk of LRTI or CAP? Since the last version of these recommendations a variety of commonly used drugs has been investigated with regard to their potential to decrease the risk of LRTI or CAP. These drugs are: inhaled steroids in COPD patients and ACE inhibitors or statins in the general population.

Inhaled steroids in COPD patients. Inhaled steroids might decrease the risk of acute exacerbation in subgroups of COPD patients, but they do not decrease the risk of LRTI. In fact, they seem to increase the risk of LTRI/CAP in COPD patients [415–419].

Statin use in the general population and the risk of CAP and death from CAP. The use of statins and/or ACE inhibitors in the general population has been investigated with regard to their potential to decrease the risk of CAP or CAP-related death.

The use of statins and/or ACE inhibitors might decrease the risk of CAP or CAP-related death in the general population. There are many more data for statins then for ACE inhibitors [420–425].

Recommendations for influenza vaccination

Should influenza vaccine be used to prevent LRTI?

1 Influenza vaccine should be given yearly to persons at increased risk of complications due to influenza [A2]. Vaccination should be carried out for immunocompetent adults belonging to one, or more, of the following categories: age >65 years, institutionalization, chronic cardiac diseases, chronic pulmonary diseases, diabetes mellitus, chronic renal diseases, haemoglobinopathies, and women who will be in the second or third trimester of pregnancy during the influenza season [8].

2 Repeated vaccinations are safe and do not lead to a decreased immune response [B1].

3 In adults, inactivated, rather than live attenuated, vaccine should be used [A1].

4 Yearly vaccination should be carried out for health care personnel, especially in settings where elderly persons or other high-risk groups are treated [B2].

5 General vaccination of all healthy adults should not be carried out in the absence of robust cost-effectiveness data for vaccination [B1] [426–441].

Recommendations for pneumococcal vaccination

Should pneumococcal vaccine be used to prevent LRTI?

1 The 23-valent polysaccharide pneumococcal vaccine prevents invasive pneumococcal disease in older persons and in other high-risk groups and should be given to all adult persons at risk for pneumococcal disease [A1].

2 Risk factors for pneumococcal disease are age >65 years, institutionalization, dementia, seizure disorders, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, history of a previous pneumonia, chronic liver disease, diabetes mellitus, functional or anatomical asplenia, and chronic cerebrospinal fluid leakage [B3]. Although smoking seems to be a significant risk factor in otherwise healthy younger adults, measures aimed at reducing smoking and exposure to environmental tobacco smoke should be preferred in this group.

3 Revaccination, once and not earlier than 5 years after primary vaccination, should be performed in asplenic patients and can be considered in the elderly and other high-risk groups [B3].

4 There are not enough data to give any recommendations concerning the use of conjugate pneumococcal vaccine in adults [442–473].

Recommendations for implementation. Active interventions should be used to enhance vaccination with either or both of the vaccines, in order to achieve an adequate vaccination coverage of the targeted population [A1] [474–477].

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