

# Guidelines for the management of adult lower respiratory tract infections - Full version

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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. Background sections and graded evidence tables are also included. The target audience for the Guideline is thus all those whose routine practice includes the management of adult LRTI.

**Keywords:** Antibiotic, community-acquired pneumonia, exacerbation of COPD, guidelines, lower respiratory tract infection

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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 (LRTI) 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 document begins with definitions and background sections on microbial cause, resistance and pharmacokinetics/pharmacodynamics, with conventional referencing. The guideline section 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. It contains the graded recommendations but also the background information for each recommendation, with details about each new cited reference and the evidence grades. 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. As this is an update using the same methodologies, the layout of the document, including text, recommendations and evidence tables, is the same as in 2005.

## 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. Thereby 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 (Appendix 1) and recommendation development and grading (Appendix 2) as in the 2005 document was used.

The document takes each clinical question for which there was a recommendation in the 2005 guidelines 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 identify 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 or 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 suggestive of 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?**

Wide variations between studies regarding the frequency of each microorganism can be explained by several factors, including differences in studied populations (e.g. age range or other risk factors), geographical area, studied samples and microbiological methods; for example, some studies focused on bacterial agents and others on viruses and intracellular bacteria. Supplementing traditional diagnostic methods with new technology-based methods could achieve higher microbial yield [18].

- 1 In the majority of studies of LRTI there is a large proportion of cases with no pathogen identified, either because the appropriate tests were not performed (as is usually the rule in outpatients) or the organism was missed. Age >70 years, renal and cardiac co-morbid illnesses and non alveolar infiltrates were independently associated with a higher proportion of unknown aetiology in 204 patients hospitalized for CAP [19].
- 2 On the other hand, multiple organisms may be found in adults, as already described in youngsters. Paediatric studies have found polymicrobial infections in CAP: dual

viral infection is present in 0–14%, dual bacterial infection in 0–14%, and mixed viral-bacterial infection in 3–30% [20].

In hospitalized adult non-immunocompromised patients, polymicrobial CAP occurred in 6–26% [21–28]. Gutierrez et al. [21] report two or more pathogens at all ages, and as well in inpatients and outpatients, the most frequent combinations being those of bacteria with an atypical organism (29%) and two bacteria (29%); patients with mixed pneumonia are likely to have more co-morbidities and a more altered outcome. Angeles Marcos et al. [23] found that the most frequent co-pathogens were *S. pneumoniae* and *C. pneumoniae*, and the most frequent combinations *S. pneumoniae* and either influenza or parainfluenza virus, and influenza virus with *C. pneumoniae*. De Roux et al. [29] reported that in the 10% of patients with mixed CAP, *S. pneumoniae* was the most prevalent microorganism; the most frequent combination was *S. pneumoniae* with *H. influenzae*; influenza virus A and *S. pneumoniae* was the most frequent association in the mixed pyogenic pneumonia group. Among the 17% of patients with mixed infections, Song et al. found 73% of patients with two different pathogens, 13% with three different pathogens and 13% with four different pathogens. The most frequent combination was *S. pneumoniae* with *C. pneumoniae* (15%). Mixed infections were found in 25% of patients with pneumococcal CAP [28]. Jennings et al. [27] found that polymicrobial infections involving bacterial and viral pathogens occurred in 15% of patients with CAP and might be associated with severe pneumonia. Johansson et al. found two or more pathogens in 35% of patients with CAP with a determined aetiology, most commonly *S. pneumoniae* together with a respiratory virus [18]. Evidence of concurrent bacterial infection was found in lung tissue specimens from 22 (29%) of the 77 US patients with fatal cases of confirmed 2009 pandemic influenza A (H1N1), including 13% caused by *S. pneumoniae* [30].

Table 1 summarizes the microbiological aetiologies of LRTI in the community. Studies have investigated the microbiological causes of CAP in outpatients (Table 2) and patients admitted to hospital (Table 3) or to the intensive care unit (Table 4). Most studies of mild infections suggest that microbial aetiologies in outpatients are similar to those in hospitalized patients [31–57].

In the community and on the regular ward, extracellular bacteria, especially *Streptococcus pneumoniae* (*S. pneumoniae*), are in first place, followed by *Haemophilus influenzae* (*H. influenzae*), *Staphylococcus aureus* (*S. aureus*) and *Moraxella catarrhalis*. Among intracellular bacilli, *Mycoplasma pneumoniae*

**TABLE 1. Aetiology of lower respiratory tract infection in the community (%). (Blank boxes indicate organism not sought)**

Reference	n	SP	HI	MC	SA	MP	CS	CPne	CB	Virus	Influenza
Boldy <i>et al.</i> [91]	42	3.0	3.0	3.0	0	8.0	0		0	21.0	10.0
Creer <i>et al.</i> 2006 [65]	80	18.8	6.3	1.2		1.2				61.3	23.8
Everett [92]	187					6.0	2.0		0	6.0	4.0
Fransen and Wolontis [93]	78	8.0	3.0		3.0	3.0				20.0	12.0
Graffelman <i>et al.</i> [94]	145	6.2	9.0	2.1		9.0	1.3			39.0	30.3
Holm <i>et al.</i> [95]	364	6	4	1	<1	3		<1		24	10
Hopstaken <i>et al.</i> [96]	247	2.9	13.8	2.9							
Macfarlane <i>et al.</i> [97]	206	30.0	8.0	2	1.0	0.5			0.5	8.0	5.0
Macfarlane <i>et al.</i> [98]	316	17.1	9.8	2.2		7.3		17.4		19.3	7.3
Shaw and Fry [99]	40	16.0	14.0		10.0	5.0	3.0		0	11.0	11.0
Range		3–30	3–14	1–3	1–10	0.5–9	0–3		0–0.5	6–61	4–30

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative bacilli; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CPne, *Chlamydomphila pneumoniae*; CPsi, *Chlamydomphila psittaci*; CB, *Coxiella burnetii*.

**TABLE 2. Aetiology of community-acquired pneumonia in the community (%). (Blank boxes indicate organism not sought)**

Reference	n	SP	HI	LP	MC	SA	GNEB	MP	CS	CPne	CPsi	CB	Virus	Influenza
Almirall <i>et al.</i> [100]	105	12.4	0	2.9		0	0	7.6	15.2	15.2	0	0	11.4	0
Almirall <i>et al.</i> [31]	232	11.6	0.4	2.2		0	0.4	3.9		9.5	0	2.2	14.2	8.2
Beovic <i>et al.</i> [101]	109	13.8	3.6	1.8	2.7	0.9		24.8		21.1	0.9			
Berntsson <i>et al.</i> [102]	54	9.3	11.1	0				37.0	3.7		3.7	0	13.0	7.4
Blanquer <i>et al.</i> [103]	48	12.5	0	12.5	0	0	0	12.5			0	0	20.8	14.6
BTS <i>et al.</i> [104]	67	6.0	0	0	0	0	0	3.0					28.0	10.0
Dulake and Selkon [105]	36	19.0	14.0			0	0	2.0				0	2	2
Foy <i>et al.</i> [106]	2256	12.0						20.0					25.0	8.0
Holm <i>et al.</i> [95]	48	15	4	0	0	2	0	8		0			13	4
Jokinen <i>et al.</i> [42]	304	41	4		3			10	12	10	1		9	2
Marrie <i>et al.</i> [49]	149							22.8		10.7		2.7		2.7
Marrie <i>et al.</i> [107]	507	5.9	4.9					15		12				
Melbye <i>et al.</i> [108]	36	11.1	0	0				13.9		8.3	0		33.3	19.4
Michetti <i>et al.</i> [52]	119	0	0	3.4		0	0	32.8	16.0	6.7	9.2	0	5.9	3.4
Miyashita <i>et al.</i> [109]	106	12.3	4.7		1.9	0.9		27.4					1.9	
Wattanathum <i>et al.</i> [25]	98	13.3	1	8.2				29.6		36.7				
Woodhead <i>et al.</i> [110]	236	36.0	10.0	0.5	0	1.0	1.0	1.0	1.0			0	13.0	8.0
Range		0–36	0–14	0–13	0–3	0–1	0–1	1–33	1–16	7–37	0–9	0–3	2–33	0–19

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CPne, *Chlamydomphila pneumoniae*; CPsi, *Chlamydomphila psittaci*; CB, *Coxiella burnetii*.

(*M. pneumoniae*) is the most common, followed in frequency by *Legionella* and *Chlamydia* species, with viruses being involved in up to 60% of community-acquired LRTI and 30% of CAP. In the intensive care unit, *S. aureus*, Gram-negative bacilli and *Legionella* spp. might be more frequently encountered. Recurrence of CAP is more likely when Gram-negative bacteria are involved, and less likely if *Legionella* spp. are involved [58].

Originally a nosocomial pathogen, methicillin-resistant *S. aureus* (MRSA) disseminated during the last decade in the community (community-acquired MRSA, CA-MRSA). Methicillin resistance is mediated by the *mecA* gene that has been associated with the Panton-Valentine leukocidin (PVL) toxin, which creates lytic pores in the cell membranes of neutrophils and induces the release of neutrophil chemotactic factors that promote inflammation and tissue destruction. New PVL-positive clones may be arising and disseminating in the community [59]. MRSA has emerged as an infectious agent of increasing frequency associated with

skin and soft-tissue infections in the community setting. However, CA-MRSA can also lead to severe pulmonary infections, including necrotizing and haemorrhagic pneumonia, pneumothorax, pneumopyothorax, empyema, ventilatory failure and septicaemia [60–63].

*Coxiella burnetii*, a Gram-negative intracellular bacterium, and a potential bioterrorism agent, is responsible for Q fever, which may have a wide variety of clinical manifestations, including flu-like syndrome, pneumonia and long-lasting fatigue syndrome. *C. burnetii* is present worldwide, cattle, sheep and goats being the most common reservoirs. Q fever occurs as endemic cases or as outbreaks in endemic areas. Outbreaks have occurred in Europe in recent decades including Switzerland, Spain, the UK, Germany and most recently, the Netherlands repeatedly since 2007, with more than 4000 notified cases [64].

The importance of viruses as causal agents has been confirmed in LRTI [65] and CAP [22,23,66]. In the majority of aetiological CAP studies looking for viruses and bacteria,

**TABLE 3.** Aetiology of community-acquired pneumonia in adults admitted to hospital (%). (Blank boxes indicate organism not sought)

Reference	n	SP	HI	LP	SA	MC	GNEB	PA	MP	CS	CPne	CPsi	CB	Virus	Influenza
Angeles Marcos et al. [23]	198	29.3	5.1	3.0	2.5	0	2.0	1.0	1.5	0.5	0.5	0	1.0	23.2	8.1
Arancibia et al. [111]	559	13.8	5.0	5.2			10.7	7.0	1.8	9.5	7.7	0.2	1.6	2.8	
Aubertin et al. [112]	274	12.4	3.3	10.6	2.2	0.0	2.9		8.8	–	–	2.6	0.7	2.6	0.0
Ausina et al. [113]	207	39.1	1.0	6.3	0.5	0.0	2.9		16.9	–	–	6.3	2.4	3.9	2.4
Berntsson et al. [114]	127	54.3	3.9	0.8	0.8	0.0	0.0		14.2	–	–	2.4	0.0	18.1	12.6
Blanquer et al. [103]	462	14.7	1.9	13.9	1.7	0.0	3.2		3.5	–	–	0.2	0.6	13.0	7.8
Blasi et al. [33]	207	7.7	2.4	4.8	3.9	1.0	5.3		8.2	10.1	10.1	0.0	0.0	–	–
Bohte et al. [34]	334	26.9	7.8	2.4	1.2	1.5	3.3		5.7	–	–	–	0.3	8.1	4.2
BTS [104]	453	34.0	5.7	2.0	0.9	0.0	0.9		17.9	–	–	2.9	1.1	7.1	7.1
Burman et al. [115]	196	32.1	4.6	2.0	1.5	1.5	1.0		8.7	–	–	3.1	0.0	21.9	8.7
Charles et al. [116]	885	14	5	3	1	1	2	2	9	2				15	8
de Roux et al. [22]	338	41	14.5	10				12						18	12
Ewig et al. [19]	204	19	6	5	2	1	6.5	4	2	10.5	10	0.5	3	3	
Falco et al. [117]	400	21.0	3.3	7.5	0.0	0.0	2.0		2.3	–	–	2.8	0.0	–	–
Falguera et al. [118]	660	34	2	5	2		3		9	16	11	1	4	5	4
Garbino et al. [119]	318	12.6	6	4.4	1.6	1.6			7.5		5.3				
GarciaVidal et al. [58]	1634	26	7	7			<1	1	1		2	1	1	<1	<1
Ginesu et al. [37]	520	10.8					32.9		0.4					0.9	
Gomez et al. [38]	342	12.6	5.6	1.5	0.0	0.3	0.0		3.2	6.1	6.1	0.0	0.0	–	–
Gutierrez et al. [120]	493 <sup>a</sup>	16.8	1.8	4.3	0.4	0.2	3.2	2.2	7.7	6.1			0.4	4.1	2.8
Holmberg [121]	147	46.9	9.5	2.7	0.7	2.0	0.0		5.4	–	–	1.4	0.0	10.9	10.2
Hone et al. [122]	50	20.0	16.0	4.0	0.0	2.0	2.0		4.0	–	–	0.0	0.0	20.0	10.0
Huang et al. [123]	389 <sup>b</sup>	3.1	20.6	0.5	1.5	0.3	6.2		10.8		4.4				
Jennings et al. [27]	304	31	11	4	2				3					31	10
Johansson et al. [18]	184	38	5	1	2	4			8					29	8
Johnstone et al. [67]	193	7	1	<1	1	2	3		2		2	0	0	15	4
Leesik et al. [124]	439	10.5	1.1		2.0	5.7	18.0	3.2	3.0		2.5				
Levy et al. [125]	116	25.9	11.2	4.3	2.6	0.9	6.9		3.4	–	–	0.9	0.0	4.3	–
Logroschino et al. [46]	613	5.9	3.6	2.8	1.1	0.8	3.9		3.3		4.2	–	–	3.1	–
Lorente et al. [47]	114	35.1	0.9	1.8	2.6	0.0	2.6		9.6		1.8	–	0.9	–	–
Macfarlane et al. [126]	127	75.6	3.1	15.0	2.4	0.0	0.8		2.4	–	–	5.5	0.8	8.7	5.5
Marrie et al. [127]	539										2.2–8.1				
McNabb et al. [128]	80	50.0	6.3	1.3	3.8	0.0	1.3		0.0	–	–	0.0	0.0	6.3	6.3
Menendez et al. [51]	184	23.9	1.6	0.5	0.0	0.0	1.6		14.1		0.5	0.0	1.1	1.6	1.6
Michetti et al. [52]	60	8.3	6.7	11.7	1.7		1.7		3.3	8.3	6.7	1.7	0.0	1.7	1.7
Miyashita et al. [109]	400	26.3	13	1.5	3.3	3.5	4	2	9.3			1.3	0.5	3	
Ortqvist et al. [129]	277	46.2	3.6	3.6	0.7	1.1	1.4		9.7	1.1	0.0	1.1	0.0	15.5	2.5
Ostergaard and Andersen 1993 [130]	254	13.8	6.3	3.1	0.4	0.8	2.0		3.9	–	–	1.2	0.0	–	–
Pareja et al. [131]	165	7.3	1.8	2.4	2.4	0.0	27.3		10.3	–	–	1.2	10.9	18.2	13.3
Ruf et al. [132]	442	15.4	2.5	3.8	2.7	0.0	2.5		9.3	–	–	3.2	0.0	8.8	4.1
Ruiz et al. [54]	395	16.5	6.3	4.3	1.8	1.0	6.3		3.3		3.8	0.5	2.8	9.9	5.8
Saito et al. [26]	232 <sup>c</sup>	24.6	18.5	3.9	3.4	2.2	1.7	0.4	5.2	8.7	6.5	2.2	0.9	16.4	
Schneeberger et al. [133]	159	11.3	10.6	2.5	3.8	3.8		8.2	12		3				
Socan et al. [55]	211	5.7	0.9	2.8	0.5	0.0	1.9		5.7		18.0	0.9	0.5	24.2	–
Sohn et al. [134]	126	13.5	0.8	2.4	0.8		12.5	3.1	6.3	7.1	7.1	0			
Song et al. [28]	955	12	6	1	2	1	6	3	6		6				
Sopena et al. [56]	330	20.3	2.1	13.9	0.6	0.0	0.3		1.5		15.8	0.0	1.2	–	–
Steinhoff et al. [57]	237	8.6					5.1		6.3		7.7			6.3	
Wattanathum et al. [25]	147	22.4	2.7	5.4	3.4		17.7	0.7	6.8		16.3				
White et al. [135]	210	11.4	1.9	1.4	3.8	0.0	1.4		14.3	–	–	1.4	2.9	14.8	12.4
Range		3–76	1–21	1–14	0–4	0–4	0–33	0–12	0–18	0–16	0–18	0–6	0–11	1–24	0–13

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; PA, *Pseudomonas aeruginosa*; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CPne, *Chlamydia pneumoniae*; CPsi, *Chlamydia psittaci*; CB, *Coxiella burnetii*.

<sup>a</sup>26.8% were outpatients.

<sup>b</sup>36.2% were outpatients.

<sup>c</sup>16% were outpatients.

viruses are the most common aetiological agents after *S. pneumoniae* [23,67].

Sporadic viral pneumonias that occurred in recent years were due to new virus, avian influenza virus, hantavirus and coronavirus. Avian influenza virus A/H5N1 infections increase the risk of a pandemic, are much more severe than routine seasonal influenza, and are associated with severe illness and a >50% mortality rate, especially in people aged 10–39 years [68,69]. The hantavirus pulmonary syndrome was recognized in 1983, but was retrospectively identified

using serological testing in patients who had a similar illness in 1959 [70]. The syndrome can result from several hantaviruses, such as Sin Nombre virus. Avoidance of areas where infected rodents live is the only preventive measure. An outbreak of severe acute respiratory syndrome (SARS) was reported in 2002, mainly in Asian countries and Canada [71,72]. New viruses belonging to the coronaviridae family were found to be responsible.

In the spring of 2009, an outbreak of severe pneumonia was reported in conjunction with the concurrent isolation of

**TABLE 4. Aetiology of community-acquired pneumonia in adults admitted to an ICU (%). (Blank boxes indicate organism not sought)**

Reference	n	SP	HI	LP	SA	GNEB	MP	CS	CPsi	CB	Virus	Influenza
Alkhayer <i>et al.</i> [136]	18	16.7	0	11.1	5.6	0	0		5.6	0	16.7	0
Almirall <i>et al.</i> [137]	58	17.2	1.7	8.6	0	6.9	0		1.7	0	1.75	–
BTS [138]	60	18.3	11.7	11.7	5	3.3	6.7	0	0	0	8.3	5.0
El Solh <i>et al.</i> [36]	57	14	7	9	7	14						2
Gowardman and Trent [39]	32	18.4			9.2	11.6						
Hirani and Macfarlane 1997 [41]	57	17.5	0	15.8	12.3	1.8	0		5.3	0	10.5	8.8
Leroy <i>et al.</i> [139]	299	26.8	8.7	0	19.1	15.1	0.7	1.7		0	–	–
Moine <i>et al.</i> [140]	132	32.6	10.6	3.0	3.8	10.6	0.8		0.8	1.5	5.35	1.5
Olaechea <i>et al.</i> [53]	262	11.5	3.8	8.0	3.8	3.1	3.1		1.5	0	1.95	–
Ortqvist <i>et al.</i> [141]	53	17.0	1.0	9.0	0	7.0	0	2.0		0	0	
Pachon <i>et al.</i> [142]	67	17.9	3.0	10.4	1.5	6.0	0	0	0	0	1.5	1.5
Paganin <i>et al.</i> [143]	112	42.9	0.9	1.8	1.8	26.8						
Rello <i>et al.</i> [144]	58	22.4	0	13.8	0	8.6	0	0	0	0	1.75	1.7
Rello <i>et al.</i> [145]	204	20.1	5.3	11.2	2.4	5.8	0.9					
Sorensen <i>et al.</i> [146]	36	33.3	8.33	8.3	8.3	2.8	0	0	0	0	13.9	2.8
Torres <i>et al.</i> [147]	92	15.2	0	14.1	1.1	9.8	6.5	0	0	0	–	–
Woodhead <i>et al.</i> [148]	50	32	0	30.0	10	0	2	0	0	0	8.0	4.0
Range		12–43	0–12	0–30	0–19	0–27	0–7	0–2	0–6	0–2	0–17	0–9

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CPsi, *Chlamydia psittaci*; CB, *Coxiella burnetii*.

novel swine-origin influenza A (H1N1) subtype viruses, which have rarely predominated since the 1957 pandemic, with features of the epidemic similar to those of past influenza pandemics. The new influenza virus was affecting a younger population, suggesting relative protection for persons who were exposed to H1N1 strains during childhood before the 1957 pandemic [73]. Severe pneumonias were reported in conjunction with the novel influenza A (H1N1) subtype virus. Pneumonias were due to the virus and to superinfection by *S. pneumoniae* or *Staphylococcus*.

Microorganisms isolated in hospitalized elderly patients with CAP are shown in (Table 5). There are large variations,

depending on the elderly threshold, where patients live and comorbidities. However, Gutierrez *et al.* [74] found that age has a strong influence on the incidence of CAP caused by the main microbial pathogens; ageing is associated with a higher risk of acquiring pneumonia by *S. pneumoniae*, influenza virus and *Chlamydia species*. Ingarfield *et al.* [75] emphasize that enterobacteriaceae accounted for more than 25% of isolates in patients older than 65 years.

Table 6 provides microbiological aetiologies of airway infection in patients with COPD exacerbation, as found in studies using various methods. Recent studies of the microbiology of acute exacerbations of chronic bronchitis found an

**TABLE 5. Microorganisms isolated in hospitalized elderly patients with community-acquired pneumonia (CAP) (%). (Blank boxes indicate organism not sought)**

Reference	n	Patients	SP	HI	LP	MC	SA	GNEB	MP	CS	CB	Virus	Influenza	Aspiration
El-Solh <i>et al.</i> [36]	57	≥80 years Home	14	7	9	4	7	17		2		2	2	
El-Solh <i>et al.</i> [36]	47	≥80 years Nursing Home	9	2	0	2	29	20		0		0		
Fernandez-Sabé <i>et al.</i> [149]	305	≥80 years Home	23	5	1			3	0.7	0.3	0	8		10
Flamaing 2003 [66]	165	≥80 years Home & Nursing Home	3.6				1.2	4.2	0.6			30.9	26.1	
Gutierrez <i>et al.</i> [21]	136	≥75 years Home	19.1	0.7	1.5	0	0	6.6	2.2	3.7		3.7	2.2	
Huang <i>et al.</i> [123]	126	≥60 years	2.4	14.3	0.8	0.8	2.4	12.7	7.1	6.3				
Jokinen <i>et al.</i> [42]	140	≥60 years Home	48	4		3			3	13		12	0	
Riquelme <i>et al.</i> [150]	101	≥65 years Home	18.8		3	1		3		8.9	5.9			
Saito <i>et al.</i> [26]	114	≥65 years Home	28.	20.2	2.6	3.5	3.5	7.9	1.8	9.6	0.9	13.2		
Zalacain 2003 [151]	503	≥65 years Home & Nursing Home	19.5	5.4	3.8	0.6	1.6	4.4	2.0	2.6	2.2	1.2	0.6	
Range			2–48	2–20	0–9	0–4	7–29	3–20	0–7	2–13	0–6	0–31	0–26	

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CB, *Coxiella burnetii*.



**TABLE 6. Aetiology of exacerbations in patients with COPD (%). (Blank boxes indicate organism not sought)**

Reference	Sample	n	SP	HI	MC	SA	GNEB	PA	MP	CS	CPne	CPsi	CB	Virus	Influenza	PI	RV	Adv	RSV
Alamoudi [78]	Sputum	139	4	12	25		9	12											
Beaty et al. [152]	Serology	44																	
Carilli et al. [153]	Serology	46							8.7						8.7	4.3	0		17.4
Eadie et al. [154]	Serology	47													4.3	2.1	23.4		0
Eller et al. [76]	Sputum	211	9	7.6	4	7.1	18.9	6.6											
Erkan et al. [155]	Sputum, Serology	75	5	35			6	1	9			17							
Fagon et al. [156]	PSB	54	8	26	3.5	4.5	6	3.5											
Groenewegen and Wouters 2003 [157]	Sputum	171	14.0	22.2	2.9		2.3	7.6											
Gump et al. [158]	Serology	116	27.6	42.24	10.3	21.6	6.9	0.8						33.6	12.9	7.8	3.4		4.3
Hutchinson et al. [81]	Sputum, Swab, Serology	148	5	11	2	2	7	6	1	2	1	1		23	2	1	18	1	1
Karnak et al. [159]	Serology	38									34.0	34.0							
Ko et al. [160]	Sputum	418	4.0	23.1	2.0	1.2	5.2	6.3											
Ko et al. [83]	Sputum, Swab, Serology	643	4	10	3	0	4	4	0				0		5	1			2
Lamy et al. [161]	Serology	49							2.0						28.6	24.5			6.1
Lieberman et al. [162]	Serology	62								11.3	11.3								
McManus 2008 [79]	Sputum	136												37	2		24	7	2
McNamara et al. [163]	Serology	42							9.5						0	0	42.8		11.9
Miravittles et al. [77]	Sputum	91	10	22	9		7	15											
Mogulkoc et al. [164]	Serology	49	8.2	8.2	6.1				6.1	22.4	22.4								
Monsò et al. [165]	PSB	29	10.3	34.5	6.9			6.9											
Murphy et al. [166]	Sputum	104			10														
Papi et al. [167]	Sputum	64	12.5	14.1	10.9	6.3	4.7	6.3						48.4	10.9	3	27		6
Roche et al. [80]	Sputum	200	8	26	6		6	9											
Rohde et al. [168]	Sputum	85												56	20	7	25		15
	Nasal lavage																		
Rosell et al. [169]	PSB	86	7	30	7	0	16	9											
Ross et al. [170]	Serology	125		0					0				0	0	10.4	1.6	3.2		
Seemungal et al. [171]	Serology	168							0	0.6	0.6				5.4	0.6	23.2		
	Culture																		
de Serres et al. [172]	Sputum, Swab, Serology	108	4	5	4	10	8	7	1					32	9	6	3		7
Soler et al. [173]	PSB	50	8.0	22.0	8.0		8.0	18.0		18.0	14.0	2.0	2.0	12.0	10.0				
Range			8–28	0–42	3–11	4–22	5–19	0–18	0–10	0–34	0.34			12–49	0–29	0–25	0–43		0–17

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; PA, *Pseudomonas aeruginosa*; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CPne, *Chlamydia pneumoniae*; CPsi, *Chlamydia psittaci*; CB, *Coxiella burnetii*; PI, Para-influenza; RI, Rhino-virus; RSV, Respiratory syncytial virus.

influence of the baseline level of lung function on pathogens (typical and atypical bacteria and/or virus) found in respiratory secretion samples [76–83]. *P. aeruginosa* should be suspected in patients who have been treated with antibiotics and in those not vaccinated against influenza [84]. Both short-term colonization followed by clearance and long-term persistence of *P. aeruginosa* are observed. While serum antibody responses do not mediate clearance of *P. aeruginosa*, mucoid strains persist in the airways [85].

The microbiological pattern of airway infection may also differ between pneumonic and non-pneumonic hospitalized exacerbations of COPD, as shown in a prospective study of 240 patients. Identification of a pathogen was more frequent in pneumonic cases (96% vs. 71%), in which *S. pneumoniae* and viruses were more frequent (43% and 78% vs. 18% and 46%, respectively) [86]. Respiratory viruses are more frequently found in induced sputum of hospitalized patients with COPD exacerbations than in control stable COPD subjects (47% vs. 10%), the most frequent viruses being rhinovirus, influenza, parainfluenza and RSV. However, if exacerbations of chronic bronchitis and/or COPD may be due to viral and/or

bacterial infection, such infections may occur without exacerbation [87]. Finally, bacterial exacerbations of COPD could be related to the appearance of new strains of *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* in the colonized airways [88].

Only a few studies assessed the microbiological pattern of airway colonization in bronchiectasis, and no study has investigated the microbiological aetiology of exacerbations. The main results for steady state bronchiectasis are provided in Table 7; they highlight the high frequency of *Pseudomonas* infection, particularly in the case of impaired lung function.

In a 2-year prospective study of 77 patients with clinically stable bronchiectasis, multivariate analysis found that early diagnosis of the disease (before 14 years of age), reduced FEV<sub>1</sub> (<80% predicted) and varicose-cystic bronchiectasis are risk factors for bronchial colonization with pathogenic bacteria, mainly *H. influenzae* and *P. aeruginosa* (odds ratio: 3.92, 3.91 and 4.80, respectively) [89]. In a study of 100 patients with steady-state bronchiectasis, the presence of *P. aeruginosa* in the sputum was associated with a lower FEV<sub>1</sub>/FVC ratio (60% vs. 72% in the absence of a pathogenic microorganism) and higher volume of daily sputum production (1–6 score: 3

**TABLE 7. Microorganisms isolated in inpatients with non-cystic fibrosis bronchiectasis (%). (Blank boxes indicate organism not sought)**

Reference	Sample	n	SP	HI	MC	SA	GNEB	PA	MP	NTM
Angrill <i>et al.</i> [89]	PSB	75	8	32		3	18	15	4	–
Chan <i>et al.</i> [174]	Sputum	32	–	19		–	53	34	–	–
Ho <i>et al.</i> [90]	Sputum	100	6	10		5	38	33	2	3
King <i>et al.</i> [175]	Sputum	89	7	47	8	4	3	12	2	2
Nicotra <i>et al.</i> [176]	Sputum	123	10.6	30.1	2.4	7.3	44	30.9	–	22.8
O'Donnell <i>et al.</i> [177]	Sputum	349	–	–		–	–	25	–	–
Range			6–11	10–32		3–7	18–53	15–33	2–4	3–23

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; PA, *Pseudomonas aeruginosa*; MP, *Mycoplasma pneumoniae*; NTM, non-tuberculous *Mycobacteria*.

vs. 1) [90]. In that study, FEV<sub>1</sub>/FVC <60% and high sputum output were independently associated with an increased risk of sputum isolation of *P. aeruginosa* (odds ratio: 3.1 and 4.7, respectively).

### Conclusion

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.

### What information is available about the frequency of antimicrobial resistance in these settings

*Streptococcus pneumoniae*. **Beta-lactams:** The prevalence of resistance to penicillin and other drugs among pneumococci has considerably complicated the empirical treatment of respiratory tract infections. Worryingly, the majority of resistant isolates are resistant to multiple classes of antimicrobials, which has a serious impact on many first-line antimicrobial therapies.

The mechanism of resistance to penicillin and other  $\beta$ -lactams is due to alterations of penicillin-binding proteins (PBP). PBPs interact with  $\beta$ -lactams enzymatically by forming a covalent complex via the active-site serine. The loss of affinity for the PBPs affects all  $\beta$ -lactams, although this may vary substantially depending on the drug. The affinity for a given  $\beta$ -lactam is different for different PBPs, and conversely, one PBP has distinct affinities for different  $\beta$ -lactams. Therefore point mutations reducing the affinity for one  $\beta$ -lactam do not necessarily affect the affinity for another compound [178]. However, National Committee for Clinical Laboratory Standards (NCCLS) guidelines state that a pneumococcal isolate that is susceptible to penicillin can be considered susceptible to other  $\beta$ -lactams. It is generally accepted that the MICs of amoxicillin and extended-spectrum cephalosporins are usually equal to or two to four times lower than the MIC of benzylpenicillin. However, pneumococci resistant to amoxicillin and

or extended-spectrum cephalosporins with the MICs of these agents equal to or 1 dilution higher than the MIC of penicillin have been identified [179].

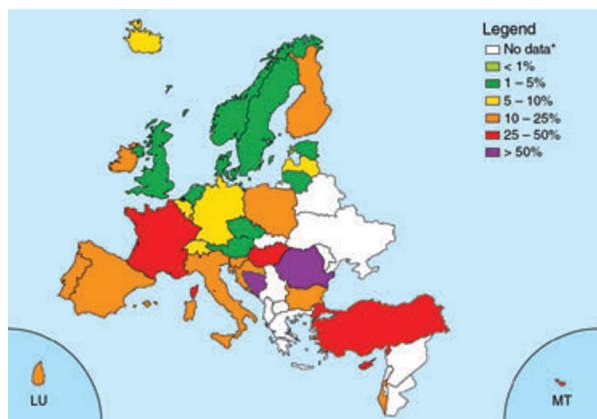
Pneumococci with decreased susceptibility to penicillin have a much higher rate of resistance to other classes of antibiotics, as has been mentioned above. Carbapenems, imipenem, meropenem and ertapenem, are the most active  $\beta$ -lactams available against PRSP. Among parenteral cephalosporins, those with good activity are cefotaxime, ceftriaxone, cefepime and ceftiofime. It is important to note that other parenteral third-generation cephalosporins are considerably less active, for example ceftizoxime and ceftazidime; the latter has been linked to a poor clinical response [180].

Amoxicillin remains the most active of all oral  $\beta$ -lactams, and among cephalosporins, cefditoren and cefpodoxime are most active, then cefuroxime and cefprozil. The use of cefuroxime in cases of bacteraemic pneumococcal pneumonia caused by penicillin non-susceptible strains has been linked to an increased mortality [181].

The prevalence of penicillin-resistant *Streptococcus pneumoniae* (PRSP) and multidrug-resistant SP varies between regions. Data on the prevalence of antibiotic resistance among *Streptococcus pneumoniae* has been regularly produced by the EARSS project, a European-wide network of national surveillance systems, providing reference data on antimicrobial resistance for public health purposes. This network receives funding from the European Commission (<http://www.earss.rivm.nl>).

In 2008, 1152 (10%) of the 11 584 invasive *S. pneumoniae* isolates reported by 32 countries were non-susceptible to penicillin (Fig. 1). Penicillin non-susceptible *S. pneumoniae* (PNSP) shows a heterogeneous picture in Europe. Most northern European countries had levels of non-susceptibility below 5%, but Finland (11%,  $n = 642$ ) and Ireland (23%,  $n = 441$ ) reported relatively high levels. High levels of PNSP, above 25%, were mainly reported from southern and eastern Europe, Cyprus (43%,  $n = 14$ ), France (30%,  $n = 557$ ), Hungary (27%,  $n = 166$ ), Malta (47%,  $n = 17$ ) and Turkey (34%,  $n = 97$ ). The level of penicillin non-susceptibility in Fin-





**FIG. 1.** *Streptococcus pneumoniae*: proportion of invasive isolates non-susceptible to penicillin (PNSP) in 2008. \*These countries did not report any data or reported <10 isolates.

land and Ireland has risen significantly from 2005. The two countries with the highest levels of PNSP in 2007 (France and Israel) showed significant decreasing rates of PNSP during the past years. Lithuania and Norway (the latter only significantly for the laboratories reporting consistently in the last 4 years) also showed decreasing trends for PNSP. In Belgium, the proportions of PNSP as well as PRSP continued to decrease significantly in 2008. In Croatia, Hungary, Ireland and Turkey a significant increase was also observed, but only for the percentage of fully resistant isolates (see Fig. 1).

The changes in the distribution of serotypes compared with 2007 were small. Serogroups 1 and 19 were still the most prevalent ones, whereas serogroup 7 and serogroup 3 became slightly more prevalent, and serogroup 14 became less prevalent in the population. The highest resistance proportions were identified in serogroups 1, 6, 9, 14, 19F and 33, of which all but 1 and 33 are included in the seven-conjugate vaccine.

Another recent survey of interest was performed in eastern and southern Mediterranean countries. Over a 36-month period, from 2003 to 2005, the ARMed project collected 1298 susceptibility test results of invasive isolates of *S. pneumoniae* from blood and spinal fluid cultures routinely processed within 59 participating laboratories situated in Algeria, Cyprus, Egypt, Jordan, Lebanon, Malta, Morocco, Tunisia and Turkey. Overall, 26% (335) of isolates were reported as non-susceptible to penicillin, with the highest proportions being reported from Algeria (44%) and Lebanon (40%) [182].

In the US, the incidence of invasive pneumococcal disease due to penicillin-resistant 19A isolates increased from 6.7% to 35% between 1998 and 2005 ( $p < 0.0001$ ). Of 151 penicillin-resistant 19A isolates, 111 (73.5%) belonged to the rapidly emerging clonal complex 320, which is related to multidrug-resistant Taiwan (19F)-14 [183]. The importance

of these findings is the high levels of penicillin resistance among strains with this serotype (amoxicillin MIC,  $\geq 4$  mg/L; cefotaxime MIC,  $\geq 2$  mg/L), and their frequent multiresistance, precluding the use of any oral  $\beta$ -lactam for the treatment of infections caused by these resistant strains.

Of special concern, is the increase in some European countries of MDR strains of serotype 19A, particularly in Spain and France [184].

The new susceptibility breakpoints for *S. pneumoniae*, published by the Clinical and Laboratory Standards Institute (CLSI) in January 2008, were the result of a re-evaluation that showed clinical response to penicillin was being preserved in clinical studies of pneumococcal infection, despite reduced susceptibility response *in vitro*. Antimicrobial susceptibility breakpoints are currently established based on (i) the pharmacokinetic and pharmacodynamic properties of an antimicrobial agent and (ii) data correlating individual MIC results with patient outcomes. Under the former criteria, susceptible, intermediate and resistant MIC breakpoints for penicillin were  $\leq 0.06$ , 0.12–1 and  $\geq 2$  mg/L, respectively, for all pneumococcal isolates, regardless of clinical syndrome or route of penicillin administration. Those breakpoints remain unchanged for patients without meningitis who can be treated with oral penicillin (e.g. for outpatient pneumonia). For patients without meningitis who are treated with intravenous penicillin, the new breakpoints are  $\leq 2$ , 4 and  $\geq 8$  mg/L, respectively.

The changes in penicillin breakpoints for *S. pneumoniae* have the potential to allow clinicians to increase use of penicillin to treat penicillin-susceptible non-meningitis pneumococcal infections, instead of using broader-spectrum antimicrobials. Its use is encouraged to prevent the spread of antimicrobial-resistant *S. pneumoniae* and also the spread of methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*, which can result from use of broader-spectrum antimicrobials [185]. In accordance with the penicillin breakpoints, the doses of suitable  $\beta$ -lactam agents for the treatment of hospitalized patients with pneumonia when *Streptococcus pneumoniae* is suspected are: penicillin G 2 g (3.2 mU) i.v. Q4 h should be adequate for strains with a penicillin MIC of  $\leq 8$  mg/L; dose to be adjusted for renal impairment; ceftriaxone 1 g i.v. or i.m. Q 12 h or cefotaxime 2 g i.v. Q6 h, should be adequate for strains with a MIC of  $\leq 8$  mg/L [186].

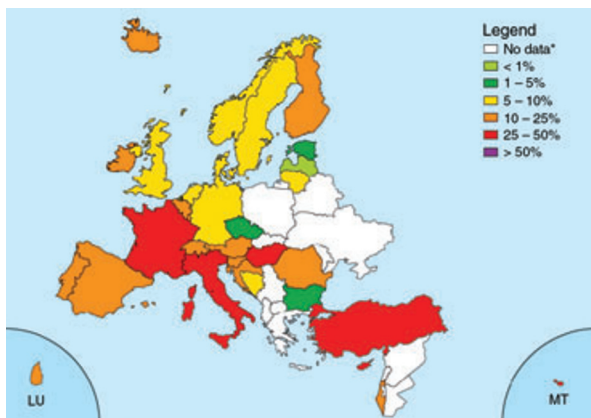
The new formulation of amoxicillin-clavulanic acid (2 g/125 mg Q12 h) available in some European countries, is able to eradicate amoxicillin-resistant strains (MICs, 4–8 mg/L), as shown in two recent randomized clinical trials (RCTs) [187].

**Macrolides:** In the EARSS database 10 982 (95%) invasive *S. pneumoniae* isolates had susceptibility results for erythromycin in 2008. From the 32 countries reporting data, 1655

(15%) isolates were reported as non-susceptible to erythromycin. Three countries reported erythromycin non-susceptibility below 5% (Czech Republic ( $n = 243$ ), Estonia ( $n = 53$ ) and Bulgaria ( $n = 24$ )). On the other hand, five countries reported non-susceptibility proportions above 25%, namely Italy (27%,  $n = 154$ ), Turkey (29%,  $n = 97$ ), France (31%,  $n = 557$ ), Hungary (32%,  $n = 158$ ) and Cyprus (29%,  $n = 14$ ). A very pronounced increase of erythromycin resistance was reported from Turkey (10% in 2005 vs. 29% in 2008) and from Ireland, only significant for the selected laboratories. The proportion of isolates non-susceptible to erythromycin in Belgium, France and the UK continued to decrease, and now also Germany, the Netherlands and Norway have reported significant decreasing rates with respect to this (see Fig. 2).

In another survey, during the same time period, the highest proportions of pneumococci that were not susceptible to erythromycin were reported from Malta (46%) and Tunisia (39%) [182].

Macrolide resistance in *S. pneumoniae* occurs by two main mechanisms: target-site modification or efflux of the drug out of the cell. The most common form of target-site modification is a specific adenine residue on the 23S rRNA (A2058) that is dimethylated by an rRNA methylase. The predominant methylase responsible for macrolide resistance in *S. pneumoniae* is encoded by *erm* (B). This methylation is thought to lead to conformational changes in the ribosome, resulting in decreased binding of all macrolide, lincosamide and streptogramin antibacterials (the so-called MLSB phenotype). The pneumococci harbouring *erm* (B) gene exhibits highs to very high levels of resistance to all macrolides, with a MIC<sub>90</sub> of both clarithromycin and azithromycin of 256 mg/L or more [188,189].



**FIG. 2.** *Streptococcus pneumoniae*: proportion of invasive isolates non-susceptible to erythromycin in 2008. From EARSS. \*These countries did not report any data or reported <10 isolates.

Macrolide efflux is mediated by the product of the *mef* (A) gene, which usually causes MICs lower than the *erm* (B) isolates (MICs of 1–32 mg/L) and retains susceptibility to clindamycin (the so-called M-phenotype) [190]. Much more rarely, mutations at different positions in domains V and II of 23S rRNA and in genes that encode the ribosomal proteins L4 and L22 have been identified as a cause of macrolide resistance [191].

Although it is not surprising that highly resistant strains (MIC,  $\geq 16$  mg/mL) may lead to clinical failure, the relevance of low-level resistance (MIC, 0.5–8 mg/mL) has been brought into question. Early this decade, a matched case-control study of patients with bacteraemic pneumococcal infections showed that breakthrough bacteraemia with an erythromycin-resistant isolate occurred in 18 (24%) of 76 patients taking a macrolide compared with none of the 136 matched patients with bacteraemia with an erythromycin-susceptible isolate [192]. These results established that macrolide resistance among pneumococci, including low level erythromycin-resistant isolates (M phenotype), is a cause of failure of outpatient pneumonia therapy. A more recent population-based case-control study from Toronto has confirmed these results [193].

Macrolide resistance contributes to an increased risk of macrolide failure, irrespective of the underlying resistance mechanism or the degree of elevation in erythromycin MIC. Therefore, it would be wise to avoid empirical macrolide therapy when a patient is at risk of being infected with a macrolide-resistant pathogen, either as a result of patient-specific characteristics or the overall rate of resistance in the community. Clinical parameters associated with macrolide resistance among pneumococci include macrolide exposure within the previous 3 months, recent use of a penicillin or trimethoprim-sulphamethoxazole, extremes of age, HIV infection and exposure to siblings colonized with resistant isolates [194].

The issue of whether the outcome of bacteraemic pneumococcal pneumonia is improved with the use of combination antibiotic therapy vs. monotherapy is still not resolved. The mechanism for the potential benefit of combining a macrolide with a  $\beta$ -lactam is uncertain, and may be multifactorial, such as providing cover for atypical pathogens, unrecognized polymicrobial infection, and/or additional cover for drug-resistant infections, synergy between these two classes of agents, and immunomodulatory properties of the macrolides. Macrolides, at sub-MICs, but not other classes of antibiotic, subvert the production of pneumolysin, even in the presence of (and irrespective of the mechanism of) macrolide resistance in *S. pneumoniae* [195].

**Fluoroquinolones:** Resistance to quinolones occurs in a stepwise fashion, with mutations being observed first in

either *parC* or *gyrA* leading to decreased fluoroquinolone susceptibility. Strains usually become fully resistant with the addition of a mutation in the other target gene (either *gyrA* or *parC*) [196]. Mutations in *parE* and *gyrB* and efflux pump are less important mechanisms of resistance.

Emergence of resistance during the course of antimicrobial therapy is most likely to develop from strains that already carry one quinolone resistance determining region (QRDR) as they require only one additional mutation in one of the other target genes to become resistant. The concept of mutant prevention concentration reflects the concentration that prevents the growth of first-step mutants. Based on their potential for restricting the selection of resistant mutants, not all fluoroquinolones are equal and can be classified accordingly; their ability to prevent the selection of mutants is in descending order: moxifloxacin, trovafloxacin, gatifloxacin, grepafloxacin and levofloxacin [197].

Fluoroquinolone resistance among *S. pneumoniae* remains rare in Europe. The use of older agents and incorrect dosing are the main drivers of resistance. The Alexander Project reported fluoroquinolone resistance among pneumococci of <1% in 2001 in northern and southern Europe (<http://www.alexandernetwork.com>). The PROTEKT study identified no quinolone-resistant isolates in northern Europe and only 1.3% of *S. pneumoniae* from southern Europe were resistant to levofloxacin (<http://www.protekt.org>). However, the prevalence of first-step mutants is largely unknown. More recent surveys suggest that the prevalence of resistance to levofloxacin and 8-methoxy fluoroquinolones (moxifloxacin, gatifloxacin) in southern Europe, specifically in Italy and Spain, appears to be around 2–3% [198].

**Tetracyclines and other agents:** In many countries of the world chloramphenicol, co-trimoxazole and tetracyclines have reached such a level and prevalence of resistance that they are no longer a good option for empirical therapy in RTI of pneumococcal aetiology. Thus, resistance to trimethoprim-sulphamethoxazole is reported in approximately 35% of isolates. Tetracycline resistance in pneumococci remains relatively high in some European countries. However, no recent comprehensive surveillance data on tetracycline resistance are available. Early this decade, among invasive isolates, up to 11.5% were reported to be resistant to tetracycline, and among non-invasive isolates, the prevalence of tetracycline resistance can be as high as 42% in southern Europe. In other European countries, recent studies have shown low resistant rates of tetracycline resistance. Thus, in the UK and Ireland, out of 1388 invasive isolates, only 4% were resistant, and among 5810 respiratory isolates, 7.6% were resistant [199].

**Haemophilus influenzae. Beta-lactams:**  $\beta$ -Lactamase production is the primary mechanism of resistance among *H. influenzae* and is a well-known predictor of treatment failure in community-acquired respiratory tract infections. This can be overcome with the use of  $\beta$ -lactamase-stable cephalosporins or  $\beta$ -lactam plus  $\beta$ -lactamase-inhibitor combinations. In addition, *H. influenzae* isolates carrying amino acid substitutions in the *ftsI* gene (encoding PBP 3) are phenotypically recognized as  $\beta$ -lactamase negative ampicillin resistant (BLNAR), which leads to the loss of susceptibility to aminopenicillin and some cephalosporins.

In Europe, resistance rates of *Haemophilus influenzae* against  $\beta$ -lactams, in spite of large inter-regional differences, seem to decline due to a decreasing number of BL-producing strains. In a recent surveillance study of antibiotic resistance in *H. influenzae*, the mean prevalence of  $\beta$ -lactam producers was 7.6%, with a range of 0.7–17.6% [200]. Although rare,  $\beta$ -lactamase-negative ampicillin-resistant (BLNAR) and  $\beta$ -lactamase-positive amoxicillin/clavulanate-resistant (BLPACR) *H. influenzae* are of concern where they exist.

**Macrolides:** Azithromycin is the most active of these agents against *H. influenzae*, with a MIC four- to eightfold lower than erythromycin (azithromycin MICs, <0.25–4 mg/L). On the other hand, the existence of efflux pumps leads to loss of susceptibility to macrolides in more than 98% of *H. influenzae* strains [201]. It appears that the vast majority (>98%) of *H. influenzae* strains have a macrolide efflux mechanism, with a few of these being hyper-resistant (1.3%; azithromycin MICs >4 mg/L) due to one or several ribosomal mutations. Occasional hypersusceptible strains (1.8%; azithromycin MICs <0.25 mg/L) are found without any underlying mechanism of resistance and appear to be the only truly macrolide-susceptible variants of *H. influenzae*.

The prevalence of resistance is based on the use of pharmacokinetic/pharmacodynamic breakpoints; large discrepancies are observed in terms of susceptibility, by use of CLSI breakpoints. So, for instance, the rate of susceptibility to clarithromycin can shift from >99% to 5% (by use of the PK/PD breakpoints).

**Fluoroquinolones and other agents:** Fluoroquinolone resistance remains rare with *H. Influenzae*.

Prevalence of tetracycline resistance: few recent data are available. A survey in the UK and Ireland showed a significant though slow downward trend ( $p < 0.00008$ ) in tetracycline non-susceptibility, which reduced from 3.5% in 1999/2000 to 1.2% in 2006/2007 and dipped as low as 0.9% in 2004/2005 [202].

In Greece, resistance to tetracycline increased from 1.6% in 1996 to 38% in 2005 [203].

Resistance to other orally administered agents, such as trimethoprim-sulphamethoxazole (TMP-SMX) and chloramphenicol, is well known. The overall frequencies of resistance to TMP-SMX remain around 18% in a recent survey in the US [204].

*Moraxella catarrhalis*. The susceptibility of *M. catarrhalis* has changed little since 1999. It is interesting to note that, despite almost universal  $\beta$ -lactamase prevalence, resistance to other antibacterial agents has not developed in *M. catarrhalis*. Clinicians should assume that all isolates of *M. catarrhalis* are resistant to amoxicillin, ampicillin, piperacillin and penicillin. Two types of  $\beta$ -lactamases can be found that are phenotypically identical: the BRO-1 and BRO-2 types. Both enzymes are readily inactivated by  $\beta$ -lactamase inhibitors, and all isolates are still susceptible to amoxicillin in combination with clavulanic acid. Other enzyme-stable  $\beta$ -lactams, macrolides and tetracyclines are still very active against *M. catarrhalis*, but rates of TMP-SMX resistance as high as 50% have been occasionally reported.

*Mycoplasma pneumoniae*. *M. pneumoniae* is inhibited by tetracyclines, macrolides, ketolides and fluoroquinolones, with little variation in MICs among clinical isolates [205,206]. Other agents that are active at the bacterial ribosome, such as streptogramins, chloramphenicol and aminoglycosides, may also show *in vitro* inhibitory activity against *M. pneumoniae* but are not normally used for therapeutic purposes against this organism. Clindamycin is active *in vitro* but its *in vivo* activity has never been demonstrated. Due to the lack of a cell wall, mycoplasmas are resistant to all  $\beta$ -lactams and glycopeptides. Sulphonamides, trimethoprim, polymyxins, nalidixic acid and rifampin are also inactive [207]. As tetracyclines and fluoroquinolones are not approved for use in children, macrolides are generally considered the treatment of choice for *M. pneumoniae* infections in both adults and children.

Since 2000, the emergence of macrolide resistance has been reported mainly in Asia. In Japan, several recent studies reported that macrolide-resistant *M. pneumoniae* isolates have been spreading since 2000, with prevalence increasing up to 30.6% according to these studies [208–210]. The A2058G mutation in domain V of 23S rRNA is the most frequent substitution associated with macrolide resistance in clinical isolates.

Data regarding current resistance patterns for *M. pneumoniae* in European adult and adolescent patients with CAP are limited. Macrolide resistance rates of 3.0% in Germany have been recently reported [211]. In France, among *M. pneumo-*

*niae*-positive specimens collected before 2005, no macrolide-resistant *M. pneumoniae* isolate was detected. In contrast, among 51 samples collected between 2005 and 2007, five (9.8%) yielded a resistant genotype, suggesting a recent increase in macrolide-resistant *M. pneumoniae* isolates in France [212]. These emerging data suggest that the epidemiological monitoring of macrolide resistance in this species has become necessary in Europe.

*Staphylococcus aureus*. In the European setting, *S. aureus* remains an unusual primary cause of CAP [213], although it is an important cause of pneumonia and death following influenza [214]. The role of CA-MRSA is even more poorly defined, although emergent in Europe [215]. Infections due to CA-MRSA have symptom onset before or within 48 h of admission to hospital and patients have no significant previous healthcare contact. CAP, which is due to CA-MRSA, classically presents in a young, previously healthy, individual with rapidly progressive, severe respiratory disease. The aggressive nature of CA-MRSA, due to toxin production, causes massive destruction in previously normal lungs.

CA-MRSA is usually only resistant to the  $\beta$ -lactams and susceptible to most other antibiotic classes. This difference in the laboratory findings may indicate that the patient has a CA-MRSA isolate as opposed to an HA-MRSA isolate. However, with time, CA-MRSA is likely to acquire the resistance genes that will make it more difficult to differentiate from HA-MRSA by routine antimicrobial susceptibility testing.

Because *S. aureus* is an uncommon cause of CAP, it does not need to be covered routinely by the empirical CAP treatment. However, the severity associated with *S. aureus* pneumonia reinforces the importance of performing routine blood and respiratory cultures in pneumonia patients.

Clindamycin and linezolid markedly suppress the formation of PVL,  $\alpha$ -haemolysin and toxic shock syndrome toxin I by suppressing translation but not transcription. Nafcillin, on the other hand, stimulates toxin production, whereas toxin levels with use of vancomycin are comparable to those in control samples not exposed to antibiotics.

As suppression of toxin production may correlate with improved outcome, vancomycin alone may not be the optimal treatment for pneumonia caused by toxin-producing CA-MRSA. Although it has not been established that the combination of a bactericidal agent with a toxin-suppressing agent, such as clindamycin or linezolid, is associated with improved outcome, it is the general feeling that vancomycin should not be used as a single agent in the treatment of CA-MRSA CAP.

In severe infections there are limited trial data to support the use of one regimen over another and recommendations



are largely based on expert advice. Adjunctive therapy, such as intravenous immunoglobulin, has been successful in some case reports, but its real contribution is unknown.

#### What new information is available about the clinical relevance of antimicrobial resistance in this setting?

The pattern of antimicrobial resistance varies between European countries. Changes in the prevalence of antibiotic resistance among the main respiratory pathogens in Europe have been reported; continued surveillance of antimicrobial resistance in all common pathogens is essential.

- 1 In pneumococci, erythromycin MICs >0.5 mg/L predict clinical failure. The prevalence of resistance 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  $\beta$ -lactams is still useful in the treatment of extrameningeal pneumococcal infections. There are no documented failures in patients with extrameningeal infections due to penicillin-resistant 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  $\leq 8$  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 a MIC of  $\leq 8$  mg/L. A new formulation of Amox/Clav (2 g/125 Q 12 h) eradicated amoxicillin-resistant strains (MICs, 4–8 mg/L) in two RCTs. 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 CA-MRSA in CAP is poorly defined, although emergent in Europe. CA-MRSA is usually only resistant to the  $\beta$ -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 *In vivo* selection of resistance means that proper use of antimicrobials is essential.

#### What new information is available about antimicrobial pharmacokinetics and pharmacodynamics

The only new information is about the need for high levofloxacin doses (750 mg OD) in the treatment of *Pseudomonas* and *Klebsiella* [216,217]. Two other new studies do not alter the current guideline recommendations [218,219].

## 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?*

**Recommendation:** 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?*

**Recommendation:** 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 (Brain Natriuretic Peptide <40 pg/mL) or N-terminal pro-BNP <150 pg/mg) make the presence of left ventricular failure unlikely [C3].

New information. Recommendation not changed.

A number of new studies on the diagnosis of cardiac failure in primary care were found, but none involving patients with a cough. The presence of hypertension and atrial fibrillation is associated with cardiac failure, and levels of BNP and NT-proBNP were found to have diagnostic value for detecting cardiac failure [220–222].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Aspromonte et al. [220]	To evaluate whether BNP measurement associated with echocardiography could effectively stratify patients with new symptoms	CSS	4A+
Mikkelsen et al. [221]	To assess diagnostic accuracy of cardiac peptides in detecting any left ventricular dysfunction (LVD) in patients referred from primary care with suspected HF before institution of medical therapy	CSS	4A+
Fuat et al. [222]	To test and compare the diagnostic accuracy and utility of B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide (NT proBNP) in diagnosing heart failure due to left ventricular systolic dysfunction in patients with suspected heart failure referred by GPs to one-stop diagnostic clinics	CSS	4A+

#### When should pulmonary embolism be considered?

**Recommendation:** 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?

**Recommendation:** 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].

One relevant study indicated that smoking and age >60 years in combination with a cough is clearly related to the presence of COPD [223]. One literature review was recently published that gave a critical report on six studies on the detection of COPD. The following signs and symptoms were mentioned at least three times in those studies: dyspnoea, wheezing (complaint), previous consultation for wheezing or cough, self-reported COPD, age, smoking, wheezing (sign), prolonged expiration and forced expiration time. The review concluded that variation and weaknesses in study designs warranted further studies [224].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Van Schayck et al. [223]	To investigate the effectiveness of case finding of patients at risk of developing chronic obstructive pulmonary disease	CSS	4A+
Broekhuizen et al. [224]	To review the literature on detection of COPD in patients with cough in primary care	MA	1C?

#### How to differentiate between pneumonia and other respiratory tract infections

**Recommendation:** 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, fever >4 days. In patients with a suspected pneumonia a test for serum-level of C-reactive protein (CRP) can be done. A CRP level of <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 the case of persisting doubt after CRP testing, a chest X-ray should be considered to confirm or reject the diagnosis [B1].

Two new studies on the diagnostic value of signs, symptoms and CRP [225,226] both showed that a combination of signs, symptoms and CRP does have diagnostic value in detecting and mainly ruling out pneumonia. Two new studies on the isolated diagnostic value of CRP confirmed the diagnostic value of CRP [227,228].

On the other hand, two reviews on the value of CRP in this field conclude that CRP has no clear diagnostic value in primary care. The review by van der Meer et al., however, found excellent positive and negative predictive values, with a ROC curve with area under the curve of 0.80. Falk et al.



concluded in their review that the isolated use of CRP will not be very useful in primary care but state nevertheless in their discussion that when a physician is in doubt about the presence of pneumonia, CRP could be helpful to rule out the disease [229,230].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Flanders et al. [227]	To evaluate the performance of a rapid, bedside whole blood C-reactive protein test as a diagnostic test for pneumonia in adults	PCS	4A+
Hopstaken et al. [225]	To assess the diagnostic value of symptoms, signs, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) for pneumonia	PCS	4A+
Van de Meer et al. [229]	To evaluate the diagnostic accuracy of C-reactive protein in detecting radiologically proved pneumonia and to evaluate how well it can discriminate between bacterial and viral infections of the lower respiratory tract.	MA	1A?
Graffelman et al. [226]	To assess the diagnostic value of signs, symptoms and CRP in detecting pneumonia	PCS	3B+
Holm et al. [228]	To evaluate the diagnostic value of CRP and procalcitonine in detecting pneumonia	PCS	3A+
Falk and Fahey [230]	To assess the diagnostic value of CRP in detecting pneumonia	MA	1A?

*Should the primary care physician test for a possible microbiological aetiology of LRTI?*

**Recommendation:** 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].

A new systematic review and two observational studies underlined these recommendations [94,228,229]. New information. Recommendation not changed.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Van de Meer et al. [229]	To evaluate the diagnostic accuracy of C-reactive protein in detecting radiologically proved pneumonia and to evaluate how well it can discriminate between bacterial and viral infections of the lower respiratory tract	MA	1A+

Graffelman et al. [94]	To evaluate the diagnostic value of medical history, physical examinations and additional tests in discriminating between viral and bacterial infections in patients with acute cough	PCS	3B+
Holm et al. [228]	To evaluate the diagnostic value of CRP and PCT in discriminating between bacterial and viral lower respiratory tract infections	PCS	3A+

#### Prognosis

*How should the risk of complications be assessed in a primary care patient with LRTI?*

**Recommendation:** 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 glucocorticoids, 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 the risk of complications [C3].

Several studies have been published, mainly on prognosis in the elderly. Some of the findings mentioned above are not yet validated externally.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Hak et al. [231]	To determine prognostic factors for complications of LRTI among elderly patients in primary care	RCS	4A+
Seppa et al. [232]	To determine which information can be used to assess the severity of LRTI in primary care	PCS	3A+
Bauer et al. [233]	To validate the CURB, CRB and CRB-65 scores for the prediction of death from community-acquired pneumonia (CAP)	PCS	3A+
Bont et al. [234]	To study predictors of complications of lower respiratory tract infections in elderly patients	PCS	3A+

Bont <i>et al.</i> [235]	To validate the CRB-65 rule for elderly patients in primary care	PCS	3A+
Bont [236]	To develop a prediction model for lower respiratory tract infections in elderly patients in primary care	PCS	3A+

## Treatment

*Should symptomatic acute cough be treated?*

**Recommendation:** Cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute LRTI in primary care [A1].

One new updated Cochrane review on cough medication concluded that there is no clear benefit from interventions [237]. Some of the studies in this review did report some beneficial effects from expectorants and antitussive agents, but these studies were small and suffered from methodological flaws. The Cochrane review on the use of bronchodilators in acute cough showed no beneficial effects [238]. One new RCT on the effects of inhaled fluticasone in patients with acute cough showed a small effect on symptom severity in the second week of disease. The clinical relevance of this small effect is, however, doubtful [239].

### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Smith <i>et al.</i> [237]	To assess the effects of oral over-the-counter cough preparations for acute cough.	MA	IA–
Smucny <i>et al.</i> [238]	To determine whether beta2-agonists improve the symptoms of acute bronchitis in patients who do not have underlying pulmonary disease.	MA	IA+
Ponsioen <i>et al.</i> [239]	To investigate the short-term effects of an inhaled steroid (fluticasone propionate (FP)) on cough	RCT	2A+

*When should antibiotic treatment be considered in patients with LRTI?*

**Recommendation:** 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 co-morbidity such as:

- 1 selected exacerbations of COPD (see section 'Exacerbations of chronic obstructive pulmonary disease');
- 2 cardiac failure;
- 3 insulin-dependent diabetes mellitus; or
- 4 a serious neurological disorder (stroke, etc.) [C3].

There is one new update of a Cochrane review on the effects of antibiotics in acute bronchitis, including one large new trial on the effects of antimicrobial therapy: no new conclusions on the overall effects on the average adult patient with acute bronchitis [240,241]. Recommendations for subgroups are based on consensus.

### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Little <i>et al.</i> [241]	To estimate the effectiveness of three prescribing strategies and an information leaflet for acute lower respiratory tract infection	RCT	2A+
Smith [240]	To assess the effects of antibiotic treatment for patients with a clinical diagnosis of acute bronchitis	MA	IA+

*What are the indications for antibiotic treatment of acute exacerbations of chronic obstructive lung disease (COPD)?*

**Recommendation:** 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.

A new Cochrane review concluded that antibiotic treatment has beneficial effects in moderately and severely ill patients with increased cough and purulence of sputum. However, the authors state that their conclusions are somewhat weakened by the considerable differences in methodology and settings between studies. The three studies in outpatients indicate that there is only a potentially beneficial effect in patients with three Anthonisen criteria [242].

### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Ram et al. [242]	To conduct a systematic review of the literature estimating the value of antibiotics in the management of acute COPD exacerbations	MA	IA+

#### Which antibiotics should be used in patients with LRTI?

**Recommendation:** Amoxicillin or tetracycline should be used as antibiotic of first choice based on least chance of harm and wide experience in clinical practice. In 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].

No clear preferences between available antibiotics can be given based on short-term benefits or frequency of side-effects. Clinical trials assessing the effects of antibiotics in primary care do vary considerably both in quality and methods regarding their reports on side-effects and adverse events in subjects. Equally, it is not really possible to compare tendencies to evoke bacterial resistance or rare, but important, side-effects. All available antibiotic agents that are active against respiratory pathogens do cause bacterial resistance. In the following recommendations the newer broad-spectrum antibiotics are reserved for second-choice escape medication when the traditional well-known agents cannot be used. Two new reviews support these recommendations [243,244].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Bjerre et al. [243]	To summarize the evidence currently available from randomized controlled trials (RCTs) concerning the efficacy of alternative antibiotic treatments for CAP in ambulatory patients above 12 years of age	MA	IA+
Mills et al. [244]	To systematically compare beta lactam antibiotics with antibiotics active against atypical pathogens in the management of community-acquired pneumonia	MA	IA+

#### Is antiviral treatment useful in patients with LRTI?

**Recommendation:** The empirical use of antiviral treatment in patients suspected of having influenza is usually not recom-

mended [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 [245,246].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Cooper et al. [245]	To review the clinical effectiveness of oseltamivir and zanamivir for the treatment and prevention of influenza A and B	MA	IA+
Jefferson et al. [246]	To review the evidence of efficacy, effectiveness and safety of registered antivirals against naturally occurring influenza in healthy adults	MA	IA+

#### How should patients with LRTI be monitored?

**Recommendation:** A patient should be advised to return if the symptoms take longer than 3 weeks to disappear.

A 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 patients 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?

**Recommendation:** 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?*

**Recommendation:** 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  $\geq 65$  as the only criterion met), hospitalization should be seriously considered [A3]. Biomarkers (e.g. CRP or PCT) have a significant potential to improve severity assessment but have not been sufficiently evaluated for the decision to hospitalize [A3].

Most recent publications have shown that the CURB-score and its modifications (particularly CRB-65 score) are comparable to the Pneumonia Severity Index index in terms of prediction of death from pneumonia in both outpatients and inpatients [233,247–254]. Moreover, the CURB-65 has been shown to outperform generic sepsis and early warning scores [255]. In view of its simplicity and the absence of any laboratory and radiographic criterion, which may not be easily available in general practice, the CRB-65 score is recommended as tool of choice in the assessment of pneumonia severity. Systolic blood pressure is the best haemodynamic predictor; diastolic pressure may be neglected [256]. The priority of clinical judgement and the need to consider non-clinical factors for decision making about treatment settings is reinforced [257–259]. In patients residing in nursing homes, a predefined clinical pathway can help to reduce hospitalization by about 50%, with comparable clinical outcomes [260].

Biomarkers (C-reactive protein (CRP)) [228,261–264], procalcitonin (PCT) [228,263,265,266], D-dimer [267], carboxy-terminal proasopressin (CT-proAVO, copeptin) [268], midregional proatrial natriuretic peptide (MR-pro-ANP) [266,269,270], midregional proadrenomedullin (MR-ADM) [271,272], and triggering receptor expressed on myeloid cells (TREM-1) [273], as well as the adrenal response [274,275], as an alternative or additional tool for the assessment of pneumonia severity, have recently gained much attention. It appears that all of them seem to have a significant potential to predict mortality. Some data suggest that predictive tools and biomarkers do not reflect identical processes and that

biomarkers may improve predictions based on clinical parameters [276,277]. However, the optimal use of clinical assessment, including severity scores and biomarkers, remains to be established. Currently, CRP and PCT are best available and may be implemented as an additional severity tool; however, the evidence is still limited. Among all biomarkers investigated, pro-ADM seems most promising [271,272].

### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

References	Objective	Design	Evidence
<b>Predictive tools</b>			
Aujesky <i>et al.</i> [250]	Reasons why emergency department providers do not rely on the pneumonia severity index to determine the initial site of treatment for patients with pneumonia	PCS	3A+
Barlow <i>et al.</i> [255]	The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia	RCS	4B+
Bauer <i>et al.</i> [233]	CRB-65 predicts death from CAP	PCS	3A+
Busing <i>et al.</i> [252]	A prospective comparison of severity scores for identifying patients with severe community-acquired pneumonia: reconsidering what is meant by severe pneumonia	PCS	3A+
Capelastegui <i>et al.</i> [251]	Validation of a predictive rule for the management of community-acquired pneumonia	PCS	3A+
Chalmers <i>et al.</i> [267]	Systolic blood pressure is superior to other haemodynamic predictors of outcome in community-acquired pneumonia	PCS	3A+
Ewig <i>et al.</i> [248]	Validation of predictive rules and indices of severity for community-acquired pneumonia	PCS	3A+
Ewig <i>et al.</i> [249]	New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality	PCS	3A+
Labarere <i>et al.</i> [257]	Factors associated with the hospitalization of low-risk patients with community-acquired pneumonia in a cluster-randomized trial	PCS	3A+
Lim <i>et al.</i> [247]	Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study	PCS	3A+
Loeb <i>et al.</i> [260]	Effect of a clinical pathway to reduce hospitalizations in nursing home residents with pneumonia: a randomized controlled trial	RCT	2A+
Man <i>et al.</i> [253]	Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong	PCS	3A+
Marrie and Huang [258]	Admission is not always necessary for patients with community-acquired pneumonia in risk classes IV and V diagnosed in the emergency room	PCS	3A+

Myint et al. [254]	Severity assessment criteria recommended by the British Thoracic Society (BTS) for community-acquired pneumonia (CAP) and older patients. Should SOAR (systolic blood pressure, oxygenation, age and respiratory rate) criteria be used in older people? A compilation study of two prospective cohorts	PCS	3A+
<b>Biomarkers</b>			
Chalmers et al. [267]	Admission D-dimer can identify low-risk patients with community-acquired pneumonia	PCS	3A+
Christ-Crain et al. [271]	Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia	PCS	3A+
Christ-Crain et al. [274]	Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia	PCS	3B+
Christ-Crain et al. [269]	Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia	PCS	3B+
Hirakata et al. [261]	Comparison of usefulness of plasma procalcitonin and C-reactive protein measurements for estimation of severity in adults with community-acquired pneumonia	RCS	4C–
Hohenthal et al. [262]	Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia	RCS	4B+
Holm et al. [228]	Procalcitonin vs. C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care	PCS	3B+
Huang et al. [272]	Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia	PCS	3A+
Menendez et al. [263]	Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia	PCS	3A+
Okimoto et al. [265]	Procalcitonin and severity of community-acquired pneumonia	RCS	4C–
Kruger et al. [266]	Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia: results from the German competence network CAPNETZ	PCS	3A+
Kruger et al. [276]	Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes	PCS	3A+
Kruger et al. [268]	C-terminal pro-vasopressin (copeptin) in patients with community-acquired pneumonia—influence of antibiotic pretreatment: results from the German competence network CAPNETZ	PCS	3A+
Prat et al. [270]	Midregional pro-atrial natriuretic peptide as a prognostic marker in pneumonia	PCS	3A+
Salluh et al. [275]	Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity	PCS	3A+
Tejera et al. [273]	Prognosis of community-acquired pneumonia (CAP): value of triggering receptor expressed on myeloid cells-1 (TREM-1) and other mediators of the inflammatory response	PCS	3B–
Thiem et al. [264]	C-reactive protein, severity of pneumonia and mortality in elderly, hospitalised patients with community-acquired pneumonia	RCS	4B+

### Who should be considered for ICU admission?

**Recommendation:** Findings reflecting acute respiratory failure, severe sepsis or septic shock and radiographic extension of infiltrates, as well as severely decompensated co-morbidities, 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 ( $\text{PaO}_2/\text{F}_i\text{O}_2 < 250$ ), involvement of >two 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.

External validation of the modified ATS rule as well as other rules (e.g. the IDSA/ATS rule [278] and SMART-COP rule [279,280]) has resulted in two important insights. First, no rule is able to account for all important severity criteria, which could justify ICU admission without substantial loss of specificity. Second, the decision to admit to the ICU is usually not exclusively based on clinical criteria but also depends on the local settings and facilities [279,281–283]. Therefore, it appears that criteria for ICU admission should be used as indicators for the need for intensified treatment (i.e. monitoring and treatment for acute respiratory failure and/or severe sepsis) rather than as advice for ICU admission.

Whereas no score has been shown to be consistently superior to others, scores relying on so-called ‘minor criteria’ should be preferred, at least for clinical use, because they avoid relying on tautological ‘major criteria’. Pneumonia severity rules such as CRB-65/CURB-65 and PSI are not useful for identifying patients with severe pneumonia.

In view of a worse prognosis in patients with a delayed transfer to the ICU as compared with direct transfer patients, close monitoring within intensified treatment should be offered to patients at risk of progressive disease. However, there is still a major need for predictors of patients who will deteriorate. The recently developed REA-ICU index still awaits validation in independent cohorts and different settings [284]. Currently, close monitoring of patients at risk within intensified treatment is the best measure to identify those patients.



Consecutive measurements of CRP and assessment of oxygenation may be used during follow-up to assess treatment response [285,286].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Brown <i>et al.</i> [281]	Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia	PCS	3B+
Bruns <i>et al.</i> [285]	Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia	PCS	3B+
Charles <i>et al.</i> [279]	SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia	PCS	3A+
Marrie and Shariatzadeh [282]	Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study	RCS	4A+
Phua <i>et al.</i> [278]	Validation and clinical implications of the IDSA/ATS minor criteria for severe community-acquired pneumonia	PCS	3A+
Renaud <i>et al.</i> [284]	Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia	PCS	3A+
Wu <i>et al.</i> [286]	Early evolution of arterial oxygenation in severe community-acquired pneumonia: a prospective observational study	PCS	3B-

*What is the value of blood cultures in the diagnosis of community-acquired pneumonia?*

**Recommendation:** Two sets of blood cultures should be performed in all patients with CAP who require hospitalization [A3].

New information. Recommendation not changed.

*S. pneumoniae* is identified in approximately 60% of positive blood cultures [287,288] and *Haemophilus influenzae* in various percentages from 2% to 13%. Other organisms are recovered in diminishing order of frequency from 14% to 2% and 1%: Gram-negative aerobes, streptococci (*S. pyogenes* and other), *Staphylococcus aureus* and mixtures of organisms [287]. For most of the latter it is difficult to decide whether they were present in the bloodstream or are skin contaminants.

In a retrospective observational cohort study of 684 hospitalized patients admitted via the Emergency Department for treatment of pneumonia [289], only 3.4% had true positive blood cultures. Combining the results of this study with six other studies, only 2.2% of >3000 patients had antibiotics changed based on positive blood cultures. This study demonstrates the limited utility of blood cultures in CAP

patients. However, it did not include many patients at risk of multidrug-resistant pathogens.

From a systematic review of 15 studies with a total of 3898 adult patients admitted with CAP, it was concluded that blood cultures rarely alter empirical antibiotic therapy, and even when there is a change, it is mostly not likely to impact patient outcome [290]. The findings of this systematic review do not support obtaining blood cultures in all adults hospitalized with CAP.

However, also in this systematic review, most investigations excluded immunocompromised or other high-risk groups, which could have biased results against blood culture utility. It would be prudent therefore not to generalize the findings.

In addition, all 15 studies included in this review were observational. Most did not prospectively require blood cultures in all patients admitted with CAP. Several studies did not explicitly require two sets of blood cultures or that blood cultures be done prior to antibiotics, so they may not have revealed the maximum utility of blood cultures. Methicillin-resistant *Staphylococcus aureus* (MRSA) previously confined to nosocomial infections has become more prevalent in the community, causing community-associated MRSA infections, including CAP [61,291]. During recent years healthy young people without traditional risk factors for *S. aureus* disease present increasingly with severe MRSA CAP associated with high mortality. Many strains contain toxin and Panton-Valentine leucocidine genes. Specimens including blood cultures should be obtained for diagnostic and antimicrobial drug susceptibility testing in order to target therapy.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Bradley [291]	Role of <i>Staphylococcus aureus</i> in CAP	MA	1A+
Hageman <i>et al.</i> [61]	Role of <i>Staphylococcus aureus</i> in CAP	RCS	4A+
Beneson <i>et al.</i> [289]	Selective use of blood cultures in emergency department pneumonia patients	RCS	4A+
Asfhar <i>et al.</i> [290]	Blood cultures for community-acquired pneumonia: are they worthy of two quality measures? A systematic review	SR	1A+

*What other invasive techniques for normally sterile specimens can be useful in the laboratory diagnosis of pneumonia?*

**Recommendation:** (a) *Thoracentesis*: diagnostic thoracentesis should be performed in hospitalized patients with CAP when a significant 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.

El Sohl studied nursing home patients requiring mechanical ventilation for suspected pneumonia and evaluated quantitative endotracheal aspirates in comparison with PSB and BAL specimens [292]. This study shows that QEA correlate well with quantitative bronchoscopic PSB and BAL. Diagnostic accuracy was most favourable at  $10^4$  CFU/mL and may be a reliable alternative to PSB or BAL in patients admitted from nursing homes requiring ventilation when bronchoscopic procedures are not feasible or available.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
El Sohl et al. [292]	Diagnostic yield of quantitative endotracheal aspirates in patients with severe nursing home-acquired pneumonia	PCS	3A+

#### What is the value of sputum examination?

**Recommendation:** *Gram stain*: 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 aetiologic bacterial species and interpretation of the results of sputum culture [A3].

New information. Recommendation not changed.

Acceptable sputum specimens can be obtained with some effort from approximately 25% of patients after inhalation of hypertonic saline to induce secretion and cough [293].

The value of the Gram stain of acceptable sputum specimens depends on the presence of a predominant bacterial

morphotype [294–296]. In a retrospective cohort study [297], sputum examination was used as a diagnostic tool in a minority of the patients, without noticeable benefit in the clinical management of CAP inpatients.

The study of Anevlavis is the first reported study to have such an amount of information concerning operating characteristics and the diagnostic value of sputum Gram stain in 1390 patients with bacteraemic CAP [298]. The sensitivity of sputum Gram stain was 82% for pneumococcal pneumonia, 76% for staphylococcal pneumonia and 79% for *Haemophilus influenzae* pneumonia, with specificities ranging from 93% to 96%. Data from this study suggest that a properly collected and read Gram stain provides a simple, readily available, rapid and inexpensive test result and can be a dependable test for the early aetiological diagnosis of bacterial pneumonia in bacteraemic patients.

Infection by *Aspergillus* spp. can be distinguished from colonization by the presence of hyphae in respiratory specimens but the diagnosis of aspergillosis is still based on the detection of circulating antigens in serum [299].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study. CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Lagerstrom et al. [293]	Good quality sputum specimens can be obtained after inhalation of hypertonic saline	PCS	3A+
Garcia Vazquez et al. [294]	The value of the presence of predominant morphotype in sputum for aetiological diagnosis of CAP confirmed	PCS	3A+
Van der Eerden et al. [295]	The value of the presence of predominant morphotype in sputum for aetiological diagnosis of CAP confirmed	PCS	3A+
Musher et al. [296]	The value of the presence of predominant morphotype in sputum for aetiological diagnosis of CAP confirmed	PCS	3A+
Uffredi et al. [299]	Diagnosis of aspergillus CAP in sputum	RCS	4B+
Signori et al. [297]	Sputum examination in the clinical management of community-acquired pneumonia	RCS	4A+
Anevlavis et al. [298]	A prospective study of the diagnostic utility of sputum Gram stain in pneumonia	PCS	3A+

**Recommendation:** *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.

Sensitivity and specificity of sputum cultures are reduced by contamination with flora colonizing the upper respiratory tract. The value of sputum cultures in establishing a bacterial

cause of LRTI depends on how the specimens are collected and processed and on whether a predominant bacterial morphotype has been observed in the Gram stain.

*What can antigen tests offer in the diagnosis of community-acquired pneumonia?*

**Recommendation:** 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 I 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 I antigen detection in urine is the most rapid method for diagnosing or excluding the infection. A negative test makes legionella unlikely, but does not exclude legionella infection [A3].

The value of the *S. pneumoniae* urinary antigen test in adults has a sensitivity of 65–100% and a specificity of 94%; however, weak positive results should be interpreted with caution. There is a relationship between the degree of the *S. pneumoniae* urinary antigen test positivity and the pneumonic severity index [300]. Therefore and for cost saving, the test could be applied in a sequential manner with reservation of the test for high-risk patients for whom demonstrative results of a sputum Gram stain are unavailable [301–310]. An *S. pneumoniae* type specific urinary antigen identifies the serotype involved [311].

Also in the prospective cohort study reported by Kobashi the pneumococcal urinary immunochromatographic test (ICT) [312] increased the diagnostic yield for pneumococcal pneumonia in patients with CAP and was particularly useful for diagnosing patients with poor quality sputum in whom antibiotic treatment nevertheless had to be selected. In this study, the authors were able to establish the clinical impact of the rapidity and simplicity of the ICT test for pneumococcal pneumonia. Pneumonia caused by *S. pneumoniae* also appeared to be treated safely and effectively with high-dose penicillin based on positive results of the urinary antigen test in the retrospective study reported by Oka [313]. Even compared with PCR on blood samples the Binax NOW *S. pneumoniae* urinary antigen test is a more sensitive and rapid test for the early diagnosis of bacteraemic pneumococcal pneumonia [314]. Persistence of *S. pneumoniae* antigenuria following diagnosis of pneumococcal pneumonia is normal and can be prolonged, especially if concentrated urine is used [315].

The effect of pretreatment with antibiotics resulted in contradictory reports: a lower detection rate in one study [295] and an increased detection rate if the test is performed 24–48 h after initiation of antibiotic treatment [316]. The urinary antigen test may also be carried out on pleural fluid with a sensitivity and specificity of 79% and 94%, respectively [307], and on serum samples with a sensitivity of 50% in bacteraemic patients and 40% in non-bacteraemic patients [317]. The ICT test performed on pleural fluid samples augments the standard diagnostic methods of blood and pleural fluid cultures, even in the case of prior antibiotic therapy, and enhances the ICT urinary antigen test: it may provide additional information beyond that obtained by the measurement of urine samples alone and vice versa [318]. Therefore this test should be considered whenever a pleural fluid sample is obtained in the setting of a parapneumonic effusion, particularly when the urinary antigen test is not contributory.

Vaccination does not result in a positive urinary antigen test [161]. Urinary antigen detection is currently the most helpful rapid test for the diagnosis of Legionella infection. The immunochromatographic format is better suited for single specimens, and produces a result within minutes. In one report different urinary antigen tests have an identical sensitivity [319]; in a second report the results of the tests differ when performed on unconcentrated urine samples but are identical when performed on concentrated urine specimens [320]. In the study by Olsen, the Binax test had a significantly higher sensitivity than the Biotest kit both for *L. pneumophila* serogroup one species and for non-*L. pneumophila* species or non-serogroup I *L. pneumophila* [321]. New Legionella antigen tests have been developed and are becoming available. They show performances comparable to that of the Binax NOW test and could be an alternative for the detection of *L. pneumophila* antigen in urine from patients suspected of having a Legionella pneumonia [322,323].

Since the urinary antigen test has been introduced, early diagnosis and treatment has helped to improve the outcomes and case fatality rate of cases involved in outbreaks of Legionellosis [324].

In Legionella infection there also exists a relationship between the degree of positivity of the urinary antigen test and the severity of the disease [325]. A positive result of the urinary antigen test, as demonstrated in the CAPNETZ study [326], is associated with a more severe clinical course and leads to a potential relevant under-recognition of species other than *L. pneumophila*.

Rapid antigen tests on respiratory specimens for the diagnosis of influenza virus infection in adult patients are too insensitive and consequently of limited value for confirming

the diagnosis when influenza is clinically suspected in adults, according to one study [327].

However, the study by Falsey [328] clearly showed that rapid influenza testing leads to reduction in antibiotic use in hospitalized adults.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study. CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Gutierrez et al. [301]	Value of <i>S. pneumoniae</i> urinary antigen test (UAT)	PCS	3B+
Smith et al. [302]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Marcos et al. [303]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Roson et al. [304]	Value of <i>S. pneumoniae</i> UAT. Proposal to apply <i>S. pneumoniae</i> UAT in high-risk patients without demonstrative Gram stain result	PCS	3A+
Ishida et al. [305]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Stralin et al. [306]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Andreo et al. [307]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Ercis et al. [308]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Genne et al. [309]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Lasocki et al. [310]	Value of <i>S. pneumoniae</i> UAT	RCS	4A+
Leeming et al. [311]	<i>S. pneumoniae</i> serotype specific EIA on urine sample	PCS	3A+
Van der Eerden et al. [295]	Value of <i>S. pneumoniae</i> UAT	PCS	3A+
Korsgaard et al. [316]	<i>S. pneumoniae</i> UAT more positive after antibiotic treatment	PCS	3A+
Andreo et al. [307]	<i>S. pneumoniae</i> UAT applicable on BAL	PCS	3A+
Dominguez et al. [317]	<i>S. pneumoniae</i> UAT applied on serum	PCS	3A+
Ortega et al. [300]	Relation between UAT and PSI	PCS	3A+
Vazquez et al. [329]	<i>S. pneumoniae</i> UAT not positive after <i>S. pneumoniae</i> vaccination	PCS	3A+
Dirven et al. [319]	Sensitivity of three UATs similar	PCS	3A+
Guerrero et al. [320]	Sensitivity of UATs different on unconcentrated samples, identical on concentrated samples	PCS	3A+
Blazques et al. [325]	Positivity of Legionella UAT related to severity of disease	PCS	3A+
Kobashi et al. [312]	Evaluating the use of a <i>Streptococcus pneumoniae</i> urinary antigen detection kit for the management of community-acquired pneumonia in Japan	PCS	3A+
Oka et al. [313]	The efficacy of high-dose penicillin for community-acquired pneumonia diagnosed by pneumococcal urine antigen test	RCS	4A+
Smith et al. [314]	Diagnosis of <i>Streptococcus pneumoniae</i> infections in adults with bacteraemia and community-acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection	PCS	3A+
Andreo et al. [315]	Persistence of <i>Streptococcus pneumoniae</i> urinary antigen excretion after pneumococcal pneumonia	PCS	3A+
Porcel et al. [318]	Contribution of a pleural antigen assay (Binax NOW) to the diagnosis of pneumococcal pneumonia	PCS	4A+
Olsen et al. [321]	Comparison of the sensitivity of the Legionella urinary antigen EIA kits from Binax and Biotest with urine from patients with infections caused by less common serogroups and subgroups of Legionella	RCS	4A+

Blanco et al. [322]	Detection of Legionella antigen in non-concentrated and concentrated urine samples by a new immunochromatographic assay	RCS	4A+
Diederer et al. [323]	Evaluation of the Oxoid Xpect Legionella test kit for detection of <i>Legionella pneumophila</i> serogroup I antigen in urine	RCS	4A+
Alvarez et al. [324]	Impact of the Legionella urinary antigen test on epidemiological trends in community outbreaks of legionellosis in Catalonia, Spain, 1990–2004	PCS	3A+
Von Baum et al. [326]	Community-acquired Legionella pneumonia: new insights from the German competence network for community acquired pneumonia	PCS	3A+
Steininger et al. [327]	Near-patient assays for diagnosis of influenza virus infection in adult patients	RCS	4A+
Falsey [328]	Impact of rapid diagnosis on management of adults hospitalized with influenza	RCS	4A+

What can serological tests offer in the diagnosis of pneumonia?

**Recommendation:** 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 betalactam 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].

Many test formats for the detection of *Mycoplasma pneumoniae*, *Chlamydomphila pneumonia* and *Legionella pneumophila* antibodies have been proposed. Several studies illustrate a lack of standardization of antigens of *Mycoplasma pneumoniae* [330–332]. In one study 6/12 and 9/12 of PCR-documented *M. pneumoniae* infections were diagnosed in acute and convalescent phase sera, respectively [333]. In another study anti-*M. pneumoniae* IgM antibodies were detected in 7–25% (depending on the test applied) of acute sera and IgG antibodies in 41–63% of convalescent sera [330]. Although IgM detection in the acute phase shows a moderate sensitivity, provided a specific test is used, a combination of IgM antibody detection and PCR may be the most sensitive approach to diagnose *Mycoplasma pneumoniae* infections, as demonstrated in the study by Martinez [334] and in the CAPNETZ study [335]. Also for acute LRTI due to *C. pneumoniae* a combination of PCR detection and specific single serum IgM measurement seems recommended [336].

Also the recent study on Legionella antibody detection confirms that the diagnosis cannot be based on one serum sample from the patient. As serology based on paired sera in most cases cannot be confirmed until rather late in the

course of the disease, it is advisable to use other diagnostic tests in combination with serology [337].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study. CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Beersma et al. [330]	Lack of standardization of antigens for <i>M. pneumoniae</i> serology of CAP. Variations in antibody detection depending on test applied	PCS	3A+
Talkington et al. [331]	Lack of standardization of antigens for <i>M. pneumoniae</i> serology of CAP	PCS	3A+
Templeton et al. [333]	Serology detects 50% and 66.6% of cases in acute and convalescent phases, respectively	PCS	3A+
Nir-Paz et al. [332]	Lack of standardization of antigens for <i>M. pneumoniae</i> serology of CAP	PCS	3A+
Martinez et al. [334]	Detection of <i>Mycoplasma pneumoniae</i> in adult community-acquired pneumonia by PCR and serology	PCS	3A+
Von Baum et al. [335]	<i>Mycoplasma pneumoniae</i> pneumonia revisited within the German Competence Network for Community-acquired pneumonia (CAPNETZ)	PCS	3A+
Hvidsten et al. [336]	<i>Chlamydia pneumoniae</i> diagnostics: importance of methodology in relation to timing of sampling	RCS	4A+
Elverdal et al. [337]	Comparison and evaluation of four commercial kits relative to an in-house immunofluorescence test for detection of antibodies against <i>Legionella pneumophila</i>	RCS	4A+

#### Are amplification tests useful for the diagnosis of LRTI?

**Recommendation:** 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 RSV 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].

Qualitative Nucleic Acid Amplification Tests (NAATs) for *S. pneumoniae* on pleural fluid, peripheral blood or sputum add little to the existing diagnostic tests in sputum and are unable to distinguish colonization from infection.

In a recent prospective study, real-time quantitative PCR (RQ-PCR) was evaluated on sputum samples from patients with CAP admitted to the hospital: the yield from RQ-PCR was almost twice as high as that from sputum culture in patients with proven pneumococcal aetiology. These figures suggest that in hospital-treated CAP patients, sputum PCR is a more sensitive method for detecting *S. pneumoniae* than sputum culture and the previously chosen cut-off level

corresponding to  $10^5$  CFU/mL is confirmed [338]. Especially when antibiotic treatment has been initiated, RQ-PCR, together with urine antigen detection, was the best method for identifying *S. pneumoniae*.

The detection of *S. pneumoniae* specific targets by real-time PCR assays, such as Spn9802 or *lytA* in plasma, is also useful for the rapid detection of bacteraemic pneumococcal pneumonia [339]. Detection of bacterial DNA load in whole blood supports the diagnosis of *S. pneumoniae* infection in patients with CAP [340]. Bacterial load is associated with the likelihood of death, the risk of septic shock, and the need for mechanical ventilation. High genomic bacterial load for *S. pneumoniae* may be a useful tool for severity assessment [341].

The ompP6-based real-time PCR for the detection of *Haemophilus influenzae* is both sensitive and specific for the detection of *Haemophilus influenzae* in respiratory secretions. Quantification facilitates discrimination between disease-causing *H. influenzae* strains and commensal colonization [342].

Quantitative PCR assays have also been shown to be useful in the diagnosis of CAP cases caused by *L. pneumophila*, although they had lower sensitivity than the urinary antigen test. Both RQ-PCR and antigen testing should be considered complementary in the diagnostic armamentarium for Legionellosis. High bacterial loads determined by RQ-PCR in LRT samples were useful for predicting disease severity, which may be an advantage of these techniques and therefore warrant further investigation [343].

NAATs for *M. pneumoniae*, *C. pneumoniae*, *L. pneumophila* and *B. pertussis*, preferably in sputum, have been further validated [333,344].

The addition of an *L. pneumophila*-specific PCR to a urinary antigen test is useful in patients with suspected Legionnaires' disease who produce sputum and might allow the early detection of a significant number of additional patients [345].

For the detection of *M. pneumoniae* CAP or LRTI cases, PCR was less sensitive than serology in one study [334] but superior to serology, especially during the early phases of infection, in another study [346]. Data analysis of different studies indicates that no single available test was reliable for the identification of *M. pneumoniae* in CAP. A combination of serology and PCR proved to be the most reliable approach for identification of *M. pneumoniae* [334,335,347].

Also for acute LRTI caused by *C. pneumoniae* a combination of PCR detection and specific single serum IgM measurement seems recommended [336].

The use of a *Bordetella pertussis* specific PCR in combination with single-serum serology [348] or the combination of culture and PCR increases the sensitivity for pertussis diagnosis [349].

The results of a recent study confirm previous findings that the addition of PCR-based methods to the conventional microbial techniques improves the yield of aetiological agents significantly and indicate that PCR is not only more rapid than conventional methods, but also more sensitive, both in aetiological diagnosis of CAP [18] and for the detection of respiratory viruses in LRTI [350–353], allowing clinicians to initiate optimal symptomatic treatment and rational use of antibiotics, adequate antiviral therapy where indicated and optimal infection control.

Previously unknown viruses have been discovered: several coronaviruses, human metapneumovirus and bocavirus. They are detected in CAP by NAATs. Reports on infection by a mixture of several viruses or infection by a mixture of viruses and bacteria exist. Systematic comprehensive studies are awaited to define the clinical importance of these viral and mixed infections.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Templeton et al. [333]	AT for <i>M. pneumoniae</i> and <i>Bordetella pertussis</i> validated	PCS	3A+
Raty et al. [344]	AT for <i>M. pneumoniae</i> validated	PCS	3A+
Johansson et al. [338]	Quantitative detection of <i>Streptococcus pneumoniae</i> from sputum samples with real-time quantitative polymerase chain reaction for aetiological diagnosis of community-acquired pneumonia	PCS	3A+
Abdeldaim et al. [339]	Usefulness of real-time PCR for <i>lytA</i> , <i>ply</i> and <i>Spn9802</i> on plasma samples for the diagnosis of pneumococcal pneumonia	PCS	3A+
Peters et al. [340]	<i>Streptococcus pneumoniae</i> DNA load in blood as a marker of infection in patients with community-acquired pneumonia	RCS	4A+
Rello et al. [341]	Severity of pneumococcal pneumonia associated with genomic bacterial load	PCS	3A+
Abdeldaim et al. [342]	Detection of <i>Haemophilus influenzae</i> in respiratory secretions from pneumonia patients by quantitative real-time polymerase chain reaction	PCS	3A+
Maurin et al. [343]	Quantitative real-time PCR tests for diagnostic and prognostic purposes in cases of legionellosis	RCS	4A+
Diederer et al. [345]	Utility of real-time PCR for diagnosis of Legionnaires' disease in routine clinical practice	RCS	4A+
Martinez et al. [334]	Detection of <i>Mycoplasma pneumoniae</i> in adult community-acquired pneumonia by PCR and serology	PCS	3A+
Nilsson et al. [346]	Polymerase chain reaction is superior to serology for the diagnosis of acute <i>Mycoplasma pneumoniae</i> infection and reveals a high rate of persistent infection	PCS	3A+
Thurman et al. [347]	Comparison of laboratory diagnostic procedures for detection of <i>Mycoplasma pneumoniae</i> in community outbreaks	PCS	3A+

Von Baum et al. [335]	<i>Mycoplasma pneumoniae</i> pneumonia revisited within the German Competence Network for Community-acquired pneumonia (CAPNETZ). <i>BMC Infect Dis</i> 9:62	PCS	3A+
Hvidsten et al. [336]	<i>Chlamydia pneumoniae</i> diagnostics: importance of methodology in relation to timing of sampling. <i>Clin Microbiol Infect</i> 15:42–49	RCS	4A+
André et al. [348]	Comparison of serological and real-time PCR assays to diagnose <i>Bordetella pertussis</i> infection	PCS	3A+
Sotir et al. [349]	Evaluation of polymerase chain reaction and culture for diagnosis of pertussis in the control of a county-wide outbreak focused on adolescents and adults	PCS	3A+
Johansson et al. [18]	Aetiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods	PCS	3A+
Mahony et al. [350]	Development of a respiratory virus panel test for detection of 20 human respiratory viruses by use of multiplex PCR and a fluid microbead-based assay	PCS	3A+
Van de Pol et al. [351]	Increased detection of respiratory syncytial virus, influenza viruses, parainfluenza viruses and adenoviruses with real-time PCR in samples from patients with respiratory symptoms	PCS	3A+
Ginocchio et al. [352]	Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak	RCS	4A+
Caram et al. [353]	Respiratory syncytial virus outbreak in a long-term care facility detected using reverse transcriptase polymerase chain reaction: an argument for real-time detection methods	PCS	3A+

#### What classification should be used for treatment?

**Recommendation:** 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].

The guidance for empirical initial antimicrobial treatment should follow three basic considerations and overall ten criteria.

#### (A) Prognostic assessment

(1) The assessment of age: patients aged  $\geq 65$  years are subdivided into those with moderate/good ability and those who are severely disabled. Ideally, this assessment should follow an established score (e.g. ADL score). Roughly, severely disabled patients may be defined as bedridden.

(2) The assessment of general prognosis: patients with pneumonia as an expected terminal event of severe co-morbidity should be managed along principles of palliative medicine.

#### (B) Assessment of correct grouping

(3) Previous hospitalizations and antimicrobial treatment: patients with hospitalizations <3 months ago and those



with repeated recent antimicrobial treatments should be classified as nosocomial pneumonia and treated accordingly.

(4) Risk factors for severe immunosuppression (i.e. at risk of opportunistic pathogens): these patients should be managed following the guidelines for immunocompromised patients.

(C) Assessment of factors determining selection of antimicrobial treatment.

(5) Severity: although severity has only a minor impact on microbial patterns, broad combination treatment is mandatory in order to cover all potential pathogens and prevent excess mortality due to treatment failure.

(6) Co-morbidity: co-morbidities may have an independent bearing on potential underlying pathogens.

(7) Residence: nursing home residence as such may not alter microbial patterns. Such risk should be assessed individually.

(8) Aspiration: may be witnessed or suspected; may correspond to gross or silent aspiration.

(9) Regional and local patterns of microbial prevalence and resistance.

(10) Considerations of tolerability and toxicity of antimicrobial agents in the individual patient.

*When should antibiotics be administered after diagnosis of pneumonia?*

**Recommendation:** 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].

As a consequence of studies suggesting an adverse prognostic effect of delayed antimicrobial treatment, immediate administration of antibiotics has been advocated in patients with CAP and suggested as an indicator of quality. Although early antibiotic treatment has been confirmed as advantageous by some authors [354], it has been heavily challenged. Some studies failed to confirm such a disadvantage of delayed antibiotic treatment [355,356]; others have questioned this practice in view of the questionable feasibility of such a policy [357], a high rate of misdiagnosis and overtreatment [358,359]. The American Academy of Emergency Medicine recommended that measurement of time to first antibiotic dose in CAP be discontinued [360]. Not all authors confirm misdiagnosis and overtreatment along with reporting antibiotic timing [358].

A distinct diagnosis of pneumonia seems mandatory before initiation of antibiotic treatment. It appears that the prognostic relevance of antibiotic timing is highest in patients at a higher risk of death.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Berjohn <i>et al.</i> [354]	Treatment and outcomes for patients with bacteraemic pneumococcal pneumonia. Medicine	PCS	3A+
Bruns <i>et al.</i> [356]	Time to first antibiotic related to composite endpoint of clinical instability, ICU admission and death	RCS	4B-
Fee and Weber [357]	Identification of 90% of patients ultimately diagnosed with community-acquired pneumonia within 4 h of emergency department arrival may not be feasible	RCS	4C-
Kanwar <i>et al.</i> [359]	Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side-effects of the 4-h antibiotic administration rule	PCS	3B-
Cheng and Buising [355]	Delayed administration of antibiotics and mortality in patients with community-acquired pneumonia	PCS	3A+
Friedberg <i>et al.</i> [358]	Reporting hospitals' antibiotic timing in pneumonia: adverse consequences for patients?	RCS	4A+
Pines <i>et al.</i> [360]	The measurement of time to first antibiotic dose for pneumonia in the emergency department: a white paper and position statement prepared for the American Academy of Emergency Medicine	Expert opinion	6C?

*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]:*

#### Recommendation:

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

<sup>a</sup>Can be applied as sequential treatment using the same drug.

<sup>b</sup>New macrolides preferred to erythromycin.

<sup>c</sup>Within the fluoroquinolones, moxifloxacin has the highest antipneumococcal activity.

In patients at risk of GNEB, particularly strains with ESBL, but without risk (or after exclusion of) of *P. aeruginosa*, ertapenem may be used.

Several publications have demonstrated that low-level pneumococcal resistance to penicillin is not associated with adverse outcomes in the treatment of patients with community-acquired pneumonia. Resistance to macrolides may be relevant in patients with moderate to severe pneumonia [361,362]. Therefore, the choice of antimicrobial agents should be based on considerations of allergy, intolerance, previous use of penicillins, macrolides or quinolones, cost and potential adverse effects rather than penicillin resistance.



Several retrospective studies suggest the superiority of a  $\beta$ -lactam-macrolide combination therapy in hospitalized patients, particularly those with more severe disease [363–365]. However, definite conclusions cannot be made from the present data [366]. Therefore, it appears that combination treatment should be restricted to patients with higher risk classes. As a rule of thumb, the more severely the patient presents, the stronger is the recommendation for such combination treatment.

There is a new formulation of amoxicillin-clavulanic acid available (2000/125 instead of 875–1000/125), which offers the advantage of higher penicillin dosing [187,367–369]. This may be particularly advantageous in patients with pneumococcal pneumonia resistant (low-level) to penicillin [187].

Respiratory quinolones are now established treatment options [363,370–379]. However, the potential small superiority of respiratory quinolones as compared with penicillin and macrolides must be balanced against concerns of selection pressure and cost [374]. Of note, because of the absence of pneumococcal coverage, ciprofloxacin is contraindicated in the treatment of community-acquired pneumonia.

The EMEA has limited the use of oral moxifloxacin. Although it was stated that ‘the benefits continue to outweigh its risks’, it is stated that it should only be prescribed when other antibiotics cannot be used or have failed. This recommendation was made mainly in view of an increased risk of adverse hepatic reactions. There is no evidence from the literature that moxifloxacin should be considered differently to levofloxacin in this regard. Moreover, there is evidence that liver toxicity is higher in amoxicillin-clavulanic acid than in respiratory quinolones [380].

Two additional agents have been investigated in patients with CAP: tigecycline [370,376,377,381] and ertapenem [382–384]. However, there are concerns about low serum levels of tigecycline at standard dosage, which might be hazardous in bacteraemic pneumonia. Ertapenem seems to be an attractive choice in patients at risk of Gram-negative enterobacteriaceae (GNEB) infection, particularly with ESBL-producing strains, but not in those at risk of *Pseudomonas aeruginosa* infection [385–388].

Regular coverage of atypical pathogens may not be necessary in non-severe hospitalized patients [244,389–391].

*Treatment options for patients with severe community-acquired pneumonia [c4] (ICU or intermediate care):*

### Recommendation:

**No risk factors for *P. aeruginosa***  
**Non-antipseudomonal cephalosporin III + macrolide<sup>a</sup>**  
 or  
 moxifloxacin or levofloxacin  $\pm$  non-antipseudomonal cephalosporin III  
**Risk factors for *P. aeruginosa***  
**Antipseudomonal cephalosporin<sup>b</sup> or acylureidopenicillin/ $\beta$ -lactamase inhibitor or carbapenem (meropenem preferred, up to 6 g possible, 3  $\times$  2 in 3-h infusion)**  
**PLUS**  
**Ciprofloxacin<sup>c</sup> OR**  
**PLUS**  
**Macrolide<sup>a</sup> + aminoglycoside (gentamicin, tobramycin or amikacin)**

<sup>a</sup>New macrolides preferred to erythromycin.

<sup>b</sup>Ceftazidime has to be combined with penicillin G for coverage of *S. pneumoniae*.

<sup>c</sup>Levofloxacin 750 mg/24 h or 500 mg twice daily is an alternative and also covers Gram-positive bacteria if treatment is empirical.

No controlled trials are available for patients treated in the ICU or meeting predictive rules for severe CAP.

Combination treatment offers an advantage over monotherapy by expanding the antimicrobial coverage [392–394] and probably by immunomodulation (macrolides, quinolones). Therefore, it should be the treatment of choice. However, respiratory quinolones may be used as monotherapy in severe pneumonia without septic shock [395–401].

The incidence of CAP through *P. aeruginosa* seems to be low [388]. In patients with risk factors for *P. aeruginosa*, meropenem offers advantages over imipenem because of the option to increase the dose significantly up to 3  $\times$  2 g [402]. Patients at risk of CAP through *P. aeruginosa* always should be treated by two antipseudomonal drugs in order to reduce the chance of inadequate treatment. After pathogen isolation and susceptibility testing, combination treatment may be de-escalated to monotherapy.

### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Alvarez-Lerma [395]	Levofloxacin in the treatment of pneumonia in intensive care unit patients	RCS	4B+
Erard et al. [396]	Full-course oral levofloxacin for treatment of hospitalized patients with community-acquired pneumonia	RCT	2A+
Van Bambeke and Tulkens [380]	Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes	MA	1A+
Frei et al. [389]	Impact of atypical coverage for patients with community-acquired pneumonia managed on the medical ward: results from the United States Community-Acquired Pneumonia Project	RCS	4A+
Mills et al. [244]	Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community-acquired pneumonia: meta-analysis	MA	1A+

Portier et al. [372]	Moxifloxacin monotherapy compared with amoxicillin-clavulanate plus roxithromycin for non-severe community-acquired pneumonia in adults with risk factors	RCT	2A+	Lin et al. [371]	An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with community-acquired pneumonia	PCS	3B+
Querol-Ribelles et al. [373]	Levofloxacin vs. ceftriaxone plus clarithromycin in the treatment of adults with community-acquired pneumonia requiring hospitalization	PCS	3C-	Lodise et al. [363]	Comparison of beta-lactam and macrolide combination therapy vs. fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia	PCS	3A+
Salkind et al. [374]	Fluoroquinolone treatment of community-acquired pneumonia: a meta-analysis	MA	1A+	Murcia et al. [386]	Clinical response to ertapenem in severe community-acquired pneumonia: a retrospective series in an elderly population	RCS	4C-
File et al. [403]	Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate (2000/125 mg) vs. those of amoxicillin-clavulanate (875/125 mg), both given twice daily for 7 days, in the treatment of bacterial community-acquired pneumonia in adults	RCT	2A+	Paladino et al. [387]	Once-daily cefepime vs. ceftriaxone for nursing home-acquired pneumonia	PCS	3A+
File et al. [187]	Efficacy of a new pharmacokinetically enhanced formulation of amoxicillin/clavulanate (2000/125 mg) in adults with community-acquired pneumonia caused by <i>Streptococcus pneumoniae</i> , including penicillin-resistant strains	MA	1B+	Schein et al. [375]	A comparison of levofloxacin and moxifloxacin use in hospitalized community-acquired pneumonia (CAP) patients in the US: focus on length of stay	RCT	3A+
Garcia et al. [392]	Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent vs. a beta-lactam agent alone	RCS	4C-	Tanaseanu et al. [376]	Integrated results of two phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia	PCS	3A+
Petitpretz et al. [368]	The efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate 2000/125 mg, twice daily, vs. oral amoxicillin-clavulanate 1000/125 mg, three times daily, for the treatment of bacterial community-acquired pneumonia in adults	RCT	2A+	Tanaseanu et al. [377]	Efficacy and safety of tigecycline vs. levofloxacin for community-acquired pneumonia	PCS	3A+
Siquier et al. [369]	Efficacy and safety of twice-daily pharmacokinetically enhanced amoxicillin/clavulanate (2000/125 mg) in the treatment of adults with community-acquired pneumonia in a country with a high prevalence of penicillin-resistant <i>Streptococcus pneumoniae</i>	RCT	2A+	Lui et al. [390]	Role of 'atypical pathogens' among adult hospitalized patients with community-acquired pneumonia	PCS	3A+
Bergallo et al. [381]	Safety and efficacy of intravenous tigecycline in the treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin	RCT	2A+	Metersky et al. [364]	Antibiotics for bacteraemic pneumonia: improved outcomes with macrolides but not fluoroquinolones	RCS	4A+
Ortiz-Ruiz et al. [382]	Ertapenem vs. ceftriaxone for the treatment of community-acquired pneumonia in adults: combined analysis of two multicentre randomized, double-blind studies	RCT	2A+	Paul et al. [366]	The need for macrolides in hospitalized community-acquired pneumonia: propensity analysis	PCS	3A+
Yakovlev et al. [384]	Ertapenem vs. cefepime for initial empirical treatment of pneumonia acquired in skilled-care facilities or in hospitals outside the intensive care unit	RCT	2A+	Vardakas et al. [379]	Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials	SMA	1A+
Martinez [393]	Monotherapy vs. dual therapy for community-acquired pneumonia in hospitalized patients	Expert opinion	4A+	Iannini et al. [361]	A case series of macrolide treatment failures in community-acquired pneumonia	RCS	4A+
Torres et al. [400]	Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study—a randomized clinical trial	RCT	2A+	Rodriguez et al. [399]	Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock	PCS	3A+
Von Baum et al. [388]	Community-acquired pneumonia through Enterobacteriaceae and <i>Pseudomonas aeruginosa</i> : diagnosis, incidence and predictors	RCS	4A+	Tessmer et al. [365]	Impact of intravenous $\beta$ -lactam/macrolide vs. $\beta$ -lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia	RCS	4C-
Vetter et al. [383]	A prospective, randomized, double-blind multicentre comparison of parenteral ertapenem and ceftriaxone for the treatment of hospitalized adults with community-acquired pneumonia	RCT	2A+	Kothe et al. [385]	Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment	PCS	3B+
Torres et al. [378]	Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia	RCT	2A+	Katz et al. [397]	Safety and efficacy of sequential i.v. to p.o. moxifloxacin vs. conventional combination therapies for the treatment of community-acquired pneumonia in patients requiring initial i.v. therapy	PCS	3A+
Dartois et al. [370]	Tigecycline vs. levofloxacin for the treatment of community-acquired pneumonia: European experience	RCT	2A+	Lode et al. [398]	Sequential i.v./p.o. moxifloxacin treatment of patients with severe community-acquired pneumonia	RCT	2A+
File [367]	Gemifloxacin once daily for 5 days vs. 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study	RCT	2A+	Martinez et al. [404]	Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteraemic pneumococcal pneumonia	RCS	4C-
				Romanelli et al. [402]	Carbapenems in the treatment of severe community-acquired pneumonia in hospitalized elderly patients: a comparative study against standard therapy	PCS	3A+
				Rzeszutek et al. [362]	A review of clinical failures associated with macrolide-resistant <i>Streptococcus pneumoniae</i>	MA	1A+
				Shefet et al. [391]	Empirical antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults	MA	1A+
				Wasserfallen et al. [401]	Cost-effectiveness of full-course oral levofloxacin in severe community-acquired pneumonia	RCT	2A+
				Weiss and Tillotson [405]	The controversy of combination vs. monotherapy in the treatment of hospitalized community-acquired pneumonia	MA	1A+

What is the recommended treatment for specific identified pathogens? Treatment for specific identified pathogens: Recommendation:

Pathogen	Recommended treatment
Highly resistant <i>S. pneumoniae</i> (>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 <i>H. influenzae</i>	Aminopenicillin plus β-lactamase inhibitor Levofloxacin Moxifloxacin
<i>Mycoplasma pneumoniae</i>	Doxycycline Macrolide Levofloxacin Moxifloxacin
<i>Chlamydia pneumoniae</i>	Doxycycline Macrolide Levofloxacin Moxifloxacin
<i>Legionella</i> spp.	Levofloxacin Moxifloxacin (most data available for levofloxacin) Macrolide (azithromycin preferred) ± rifampin
<i>Coxiella burnetii</i>	Doxycycline Levofloxacin Moxifloxacin
<i>Acinetobacter baumannii</i>	Third-generation cephalosporin + aminoglycoside Ampicillin-sulbactam
No experience in pneumonia for tigecycline.	

There is still no convincing evidence that discordant treatment of penicillin-resistant pneumococci negatively affects clinical outcome [186,406–409]. Thus, penicillin may still be used as a targeted treatment in pneumococci resistant up to MIC 4 mg/L.

Recent publications have confirmed that respiratory quinolones, particularly levofloxacin, offer advantages over macrolide treatment for *Legionella* infection. If a macrolide is used, azithromycin is the preferred drug. The superiority of levofloxacin and azithromycin is most relevant in patients with severe Legionellosis [410–412].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Aspa et al. [406]	Drug-resistant pneumococcal pneumonia: clinical relevance and related factors	PCS	3A+

Bonnard et al. [407]	Community-acquired bacteraemic pneumococcal pneumonia in adults: effect of diminished penicillin susceptibility on clinical outcome	PCS	3B?
Falco et al. [408]	Influence of penicillin resistance on outcome in adult patients with invasive pneumococcal pneumonia: is penicillin useful against intermediately resistant strains?	PCS	3A+
Lujan et al. [409]	Prospective observational study of bacteraemic pneumococcal pneumonia: effect of discordant therapy on mortality	PCS	3B?
Plouffe et al. [410]	Azithromycin in the treatment of <i>Legionella pneumoniae</i> requiring hospitalization	PCS	3A+
Sabria et al. [411]	Fluoroquinolones vs. macrolides in the treatment of Legionnaires disease	PCS	3A+
Yu et al. [412]	Levofloxacin efficacy in the treatment of community-acquired legionellosis	MA	1A+
Peterson et al. [186]	Penicillins for treatment of pneumococcal pneumonia: does <i>in vitro</i> resistance really matter?	MA	1A+

What should be the duration of treatment?

**Recommendation:** The duration of treatment should generally not exceed 8 days in a responding patient [C2]. Biomarkers, particularly PCT, may guide shorter treatment duration.

The focus of recent studies dealing with treatment duration has been the assessment of post-discharge outcomes. European authors report a declining duration of hospitalization (and therefore i.v. treatment) [413]. Co-morbidity, particularly cardiopulmonary and neurological conditions, has been associated with rehospitalizations but not treatment failures due to inadequately short (i.v.) treatment duration [414]. On the other hand, ongoing clinical inflammation despite clinical recovery has been described [415]. However, it is improbable that the level of inflammation can be influenced by prolonged treatment duration.

Most patients with hospitalized non-severe pneumonia are appropriately treated with 7 days of antibiotics. Although there is only one study addressing treatment duration in nosocomial pneumonia, it appears reasonable to believe that treatment duration for severe pneumonia should not be different from nosocomial pneumonia. According to this study, 8 days appears to be comparable to 15 days of treatment. However, in the presence of *P. aeruginosa* and other non-fermenters, clinicians must be aware of an increased risk of relapses [416].

Recently, biomarkers have been described as useful tools to safely reduce antibiotic treatment duration. Biomarkers can guide treatment duration by the application of predefined stopping rules for antibiotics [417–419]. It has been shown that such rules work even in most severe cases, including pneumonia with septic shock, and even if clinicians are allowed to overrule the predefined stopping rule [420,421].

## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Bouadma <i>et al.</i> [420]	Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomized controlled trial	RCT	2A+
Capelastegui <i>et al.</i> [413]	Declining length of hospital stay for pneumonia and post-discharge outcomes	PCS	3B-
Chastre <i>et al.</i> [416]	Comparison of 8 vs. 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. <i>JAMA</i> 2003; <b>290</b> (19):2588-2598. Ref ID: 4116	RCT	2A+
Christ-Crain <i>et al.</i> [417]	Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial	RCT	2B+
El Moussaoui <i>et al.</i> [422]	Comparison of 3 days with 8 days of intravenous amoxicillin	RCT	2A+
Jasti <i>et al.</i> [414]	Causes and risk factors for rehospitalization of patients hospitalized with community-acquired pneumonia	PCS	3A+
Kristoffersen <i>et al.</i> [418]	Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission—a randomized trial	RCT	2A+
Nobre <i>et al.</i> [421]	Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial	RCT	2A+
Schuetz <i>et al.</i> [419]	Effect of procalcitonin-based guidelines vs. standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial	RCT	2A+
Yende <i>et al.</i> [415]	Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis	PCS	3A+

*When should i.v. treatment be used and when should the switch to oral occur?*

**Recommendation:** 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].

The efficacy and safety of early switch therapy has been confirmed by several studies and meta-analyses [423,424]. Hospitalized patients with non-severe pneumonia, no sepsis and no reason for impaired intestinal absorption are candidates for oral treatment from the beginning [425]. Switch

therapy is safe and may be guided by an algorithm [426] or pathway [427]. The routine practice of in-hospital observation after the switch from i.v. to oral antibiotics for patients with CAP may be avoided [428]. Also in patients with severe pneumonia, switch to oral antimicrobial treatment after 3 days of intravenous treatment and treatment response is safe [429].

## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Athanassa <i>et al.</i> [423]	Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis	MA	1A+
Lee and Lindstrom [424]	Early switch to oral antibiotics and early discharge guidelines in the management of community-acquired pneumonia	PCS	3B+
Marras <i>et al.</i> [425]	Efficacy of exclusively oral antibiotic therapy in patients hospitalized with non-severe community-acquired pneumonia: a retrospective study and meta-analysis	RCS + MA	4B + 1B+
Nathan <i>et al.</i> [428]	In-hospital observation after antibiotic switch in pneumonia: a national evaluation. <i>Am J Med</i> 2006; <b>119</b> : 512-517. Ref ID: 603	PCS	3A+
Oosterheert <i>et al.</i> [429]	Effectiveness of early switch from intravenous to oral antibiotics in severe community-acquired pneumonia: multicentre randomized trial. <i>BMJ</i> 2006; <b>333</b> : 1193-1196. Ref ID: 32	RCT	2A+
Shindo <i>et al.</i> [427]	Implication of clinical pathway care for community-acquired pneumonia in a community hospital: early switch from an intravenous beta-lactam plus a macrolide to an oral respiratory fluoroquinolone	RCS	4A+
van der Eerden <i>et al.</i> [426]	Evaluation of an algorithm for switching from i.v. to p.o. therapy in clinical practice in patients with community-acquired pneumonia	PCS	3A+

*Which additional therapies are recommended?*

**Recommendation:** All patients should be subject to early mobilization [A3].

Low molecular 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 [A3].

Early mobilization has been shown to be associated with better outcome. For the purpose of the study, early mobilization was defined as movement out of bed with change from horizontal to upright position for at least 20 min during the first 24 h of hospitalization, with progressive movement each subsequent day during hospitalization [430].

Several studies indicate that non-invasive ventilation (NIV) may also work in patients with pneumonia, particularly in patients with COPD [431,432]. Non-invasive ventilation has been shown to reduce intubation in patients with ARDS in 54% of treated cases [433]. It may be feasible and also effective in do-not-intubate patients [434] and, therefore, may be an option even in palliative care.

Despite one promising controlled trial [435], two meta-analyses show that at present steroids cannot be recommended in the treatment of patients with CAP [436,437].

One meta-analysis failed to find an effect for the following interventions: activated protein C, non-invasive mechanical ventilation, anticoagulants, immunoglobulin, granulocyte-colony-stimulating factor, statins, probiotics, chest physiotherapy, antiplatelet drugs, over-the-counter cough medications, beta(2)-agonists, inhaled nitric oxide and angiotensin-converting enzyme inhibitors [438].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Antonelli et al. [433]	A multiple-centre survey on the use in clinical practice of non-invasive ventilation as a first-line intervention for acute respiratory distress syndrome	PCS	3A+
Bulow and Thorsager [434]	Non-invasive ventilation in do-not-intubate patients: 5-year follow-up on a 2-year prospective, consecutive cohort study	RCS	4B+
Confalonieri et al. [435]	Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study	RCT	2C-
Confalonieri et al. [431]	Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of non-invasive ventilation	RCT	2B+
Ferrer et al. [432]	Non-invasive ventilation in severe hypoxaemic respiratory failure: a randomized clinical trial	RCT	2B+
Gorman et al. [436]	Corticosteroid treatment of severe community-acquired pneumonia.	MA	1A+
Mundy et al. [430]	Early mobilization of patients hospitalized with community-acquired pneumonia. <i>Chest</i> 2003; 124(3):883-889. Ref ID: 4438	PCS	3A+
Salluh et al. [437]	The role of corticosteroids in severe community-acquired pneumonia: a systematic review	MA	1A+
Siempos et al. [438]	Adjunctive therapies for community-acquired pneumonia: a systematic review	MA	1A+

*When should aspiration pneumonia be suspected?*

**Recommendation:** 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].

#### Evidence Table

MA, meta-analysis (or systematic review), RCT, randomized controlled trial, PCS, prospective cohort study, RCS, retrospective cohort study, CCS, case-control study, CSS, cross-sectional study, SR, systematic review

#### Table of evidences

Reference	Objective	Design	Evidence
Adams et al. [439]	To assess role of lipid laden macrophages in diagnosis	PCS	3B+
Chen et al. [440]	Study of pneumonia in patients with dementia	RCS	2B+
DeToledo et al. [441]	To assess AP frequency after epileptic fits	RCS	4A+
El Solh et al. [6]	BAL study of microbiology of nursing home patients	PCS	4A+
Kadowaki et al. [442]	Antibiotic trial	RCT	2B+
Leroy et al. [44]	Study of ICU admissions	RCS	4B+
Mier et al. [443]	PSB study of ICU admissions	PCS	3B+
Mylotte et al. [444]	To compare features of aspiration pneumonia (AP) with aspiration pneumonitis	RCS	4A+
Reza et al. [445]	To compare features of AP in patients from long-term care facilities and the community	RCS	4A+
Teramoto et al. [446]	To identify frequency of aspiration pneumonia in hospitalized adults with CAP	PCS	3B?

*What empirical antibiotic treatment is recommended for aspiration pneumonia?*

#### Recommendation:

Hospital ward, admitted from home	ICU or admitted from nursing home
<b>Oral or i.v. <math>\beta</math>-lactam/<math>\beta</math>-lactamase inhibitor or Clindamycin or i.v. cephalosporin + oral metronidazole or moxifloxacin</b>	<b>Clindamycin + cephalosporin or Cephalosporin + metronidazole</b>

Studies (mainly of clindamycin vs. a comparator antibiotic) have mainly included only small numbers of patients (<40 per treatment arm) and do not reach consistent conclusions regarding the superiority of one antibiotic regime over another [442,447-451]. In one larger open RCT, clinical response was identical in those treated with moxifloxacin and those treated with ampicillin-sulbactam, but a significant difference could have been missed due to lack of blinding and because target recruitment was not achieved [452]. Our recommendation is based on knowledge of likely causative pathogens [6,44,443] and the antibiotic regimes used in these studies.



## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Table of evidences

Reference	Objective	Design	Evidence
Allewelt et al. [447]	Ampicillin/sulbactam vs. clindamycin + cephalosporin	RCT	2B-
Bartlett and Gorbach [448]	Penicillin G vs. clindamycin in anaerobic infection	RCT	3B+
El Solh et al. [6]	BAL study of microbiology of NH patients	PCS	4A+
Fernandez Sabe et al. [449]	Co-amoxiclav in anaerobic infection	PCS	3B+
Gudiol et al. [450]	Clindamycin vs. penicillin	RCT	2B+
Kadowaki et al. [442]	Ampicillin/sulbactam vs. clindamycin vs. panipenem/betamiprom	RCT	2B-
Leroy et al. [44]	Study of ICU admissions	PCS	4B+
Mier et al. [443]	PSB study of ICU admissions	PCS	3B+
Ott et al. [452]	Comparison of moxifloxacin vs. ampicillin/sulbactam	RCT	2C-
Perlino [451]	Clindamycin vs. metronidazole	RCT	3B-

*How should response be assessed and should chest radiograph be repeated?*

**Recommendation:** 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 radiographic resolution, requires longer time periods. C-reactive protein should be measured on days 1 and 3/4, 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].

Repeated daily measurement of the PSI found a rising PSI to be related to mortality in one study, but is not practical in routine practice [453].

A number of studies have used C-reactive protein levels on admission [454] and repeated measurements after admission, both for all admissions [262,285,454,455] and those admitted to the ICU [456], to predict clinical outcome. Measurement of CRP on day 3 [285,454] or day 4 [262,455] appears to be most useful. Failure of CRP to fall by 50% by day 4 was associated with fivefold increase in mortality, ventilation and complications [455].

Procalcitonin may also be useful but has not been sufficiently studied to make a recommendation [454].

## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS,

retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Bruns et al. [285]	To study relation between day 3 and 7 CRP levels and inappropriate antibiotic therapy	PCS	3C+
Chalmers et al. [455]	To study CRP as severity predictor in CAP	PCS	3A+
Chen et al. [453]	To assess value of repeated PSI measurement as mortality predictor	PCS	3A+
Coelho et al. [456]	To study relationship between CRP and clinical course of CAP on the ICU	PCS	3A+
Hohenthal et al. [262]	To study relationship between daily CRP and complications in CAP	PCS	3A+
Menendez et al. [454]	Study of relationship between cytokines and treatment failure	PCS	3A+

*How should the non-responding patient be assessed?*

**Recommendation:** 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. 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/her individual risk factors [C3].

**Exacerbations of chronic obstructive pulmonary disease**

*Which hospitalized patients with COPD exacerbations should receive antibiotics?*

**Recommendation:**

- 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.



Fever is not observed in 30% of exacerbations [457]. The relationship between purulence and bacterial growth is confirmed in one study [458]. In addition, a bronchoscopic study found that referred purulence by the patient had a sensitivity of 89.5%, a specificity of 76%, a predictive positive value of 77% and a negative predictive value of 89% to detect bacteria in protected specimen brush bronchoscopic samples in COPD hospitalized patients with exacerbation [459].

However, small studies found a weak association between sputum purulence and bacterial load [460] or bacterial growth [461]. In this later study Gram stain of sputum was the best indicator of bacterial infection. Randomized-controlled trials are needed to clarify which COPD exacerbated patients requiring hospitalization would benefit from antibiotics. Biomarkers such as procalcitonin may help to detect those exacerbations requiring antibiotics but the information available comes from a single-centre randomized study [462].

In one case-control study of AECOPD, viruses were found in an important percentage of AECOPD patients requiring hospitalization [168]. In one study focusing on *Mycoplasma pneumoniae*, this microorganism was involved in 32% of hospitalizations [463].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Allegra et al. [458]	To study the relationship between objective purulence and the presence of bacteria	PCS	3B+
Lieberman et al. [457]	To study the frequency of fever in exacerbations	PCS	3C+
Rohde et al. [168]	A case control study to investigate the role of different viruses on acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	CCS	3C+
Lieberman et al. [463]	To study the role of <i>Mycoplasma pneumoniae</i> in hospitalized patients with AECOPD	PCS	2C+
Soler et al. [459]	To study the association between purulence and bacterial bronchoscopic samples	PCS	3A+
Brusse-Keizer et al. [460]	To study the association between sputum colour and sputum bacterial load	PCS	3C-
Burley et al. [461]	To study the association between symptoms and Gram stain and sputum bacterial growth	PCS	3B+
Stolz et al. [462]	To study the value of procalcitonin to decrease the use of antibiotics in exacerbated COPD	RCT	2A+

What stratification of patients with COPD exacerbation is recommended in order to direct treatment?

#### Recommendation:

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.

It is confirmed that *P. aeruginosa* is associated with a small percentage of exacerbations that need hospitalization [157,160]. *P. aeruginosa* exacerbations seem to be independent of the bronchial bacterial load [169]. *P. aeruginosa* represented the 17% of isolated microorganisms in 328 out of 494 episodes in Taiwan. The isolation of *P. aeruginosa* was associated with poorer outcome [464]. In a case-control study the isolation of multidrug-resistant microorganisms in AECOPD, including *P. aeruginosa*, was associated with higher mortality [465].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Groenewegen and Wouters [157]	To study bacterial infections in COPD exacerbated patients that need hospitalization	PCS	3C+
Ko et al. [160]	To study sputum microbiology in AECOPD	PCS	4C+
Rosell et al. [169]	To study the microbiological determinants of AECOPD	MA	1A+
Lin et al. [464]	To study the microbiology of AECOPD	PCS	3B+
Montero et al. [465]	To study the association between multi-resistant <i>P. aeruginosa</i> and outcome of AECOPD	CCS	4b+

What are the risk factors for *P. aeruginosa*?

#### Recommendation:

*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 (FEV<sub>1</sub> < 30%) [A3].
- 4 Oral steroid use (>10 mg of prednisolone daily in the last 2 weeks) [A3].

One study has investigated [84] the risk factors for *P. aeruginosa*. Prior use of antibiotics was a risk factor for *P. aeruginosa* infection (OR 6.06). Influenza vaccination was a protective factor (OR 0.15). We do not know the negative predictive value of this finding. A study of 193 patients with acute exacerbation identified the following variables as independent

predictors of Gram-negative bacilli and *P. aeruginosa* infection: FEV<sub>1</sub> < 35% of predicted value, systemic steroid use and prior antibiotic therapy within the preceding 3 months. The negative predictive value of this rule was 89% [466]. A recent study from Garcia Vidal *et al.* [467] found that the risk factors for *P. aeruginosa* in the initial sputum were the BODE index, admissions in the previous year, systemic steroid treatment and previous isolation of *P. aeruginosa*.

However, in a very large retrospective study *P. aeruginosa* was found independently of the severity (uncomplicated AECOPD vs. complicated AECOPD; 6% vs. 9.4%) [468].

Despite the fact that recommendations for treating *Pseudomonas aeruginosa* remain unchanged in these guidelines, some members of the panel disagreed about covering *Pseudomonas aeruginosa* as initial empirical treatment in patients at risk. The rationale behind this disagreement lies in the studies that consider that *P. aeruginosa* is a colonizer and not a pathogen.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Monsó <i>et al.</i> [84]	To study the risk factors for bacterial exacerbations	PCS	3C+
Lode <i>et al.</i> [466]	To study the risk factors for bacterial aetiology in AECOPD	PCS	3B+
Garcia-Vidal <i>et al.</i> [467]	To study the risk factors for <i>P. aeruginosa</i> isolation in AECOPD	PCS	3B+
Kahn <i>et al.</i> [468]	To study the entry microbiological criteria in antibiotic trials of AECOPD	RCT	4B+

*Which microbiological investigations are recommended for the hospitalized patient with COPD exacerbation?*

**Recommendation:** 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.

*Is there new information about pathogens associated with COPD?* Most bacterial isolates from patients with COPD are *Streptococcus pneumoniae* and *Haemophilus influenzae*, but *Moraxella catarrhalis* has recently been shown to be associated with approximately 10% of all exacerbations of COPD [166]. In the case of *H. influenzae*, it is now clear that patients can be colonized by an identical strain of *H. influenzae* over extended periods of time despite intermittent cultures being

negative for the colonizing (or any other) *H. influenzae* strain [469]. Over the course of the lifetime of a COPD patient, the flora associated with exacerbations does change. In severe cases with FEV<sub>1</sub> < 50% of normal, Gram-negative flora, including *P. aeruginosa*, become increasingly important as associated pathogens [458]. Acquisition of a new strain of *P. aeruginosa* is associated with exacerbations [85,458].

*Is there a causal relationship between infections and exacerbations of COPD?* Purulent sputum is almost always associated with significantly positive cultures [458]. A causal relationship between infections and exacerbations of COPD has not been established but the association between the two is very strong. In a prospective analysis of COPD patients with exacerbations requiring hospitalization, Papi *et al.* [167] showed that the frequency of isolation from sputum of bacteria and viruses was much higher during exacerbations than during stable periods, and that eosinophilia within sputum was higher in viral infections. Furthermore, in a longitudinal study of bacterial load in sputum amongst patients with COPD, the FEV<sub>1</sub> decline was mirrored by an increase in sputum bacterial load [470]. A recent detailed longitudinal study found that quantitative counts of established sputum flora do not greatly change between stable and exacerbation periods in COPD patients [471]. Sethi *et al.* [472] have demonstrated that during exacerbations of COPD caused by *H. influenzae* there is a specific immune response to the infecting strain of *H. influenzae*.

*Does PSI sampling increase the diagnostic yield over other respiratory tract samples?* In patients with cystic fibrosis, PSI sampling does not increase the culturable yield of *P. aeruginosa* over regular sputum sampling [473].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Aaron <i>et al.</i> [473]	To determine if PSI of biofilms of cystic fibrosis patients yields additional <i>P. aeruginosa</i> isolates cf sputum culture	PCS	3A? small numbers
Allegra <i>et al.</i> [458]	Colorimetric and detailed microbiological assessment of sputum in a large sample of COPD patients of varying clinical severity	PCS	3A+
Murphy <i>et al.</i> [166]	To establish causal link viz AECOPD and <i>Moraxella</i> in a longitudinal cohort with molecular microbiological testing of sputum and serology	PCS	3A? there have been previous studies that found little evidence of moraxella involvement

Murphy et al. [469]	Longitudinal molecular analysis of <i>H. influenzae</i> isolates from sputum	PCS	3A+
Papi et al. [167]	Prospective study of diagnostic yield from sputa from patients during and after exacerbations of COPD	PCS	3A+
Sethi et al. [472]	Longitudinal study of COPD patients including detailed analysis of serological responses during exacerbations	PCS	3A+
Wilkinson et al. [470]	Correlation of sputum bacterial load with clinical features and severity of longitudinal series of COPD patients	PCS	3A+
Sethi et al. [471]	Detailed longitudinal study of quantitative sputum counts comparing stable and exacerbation periods	PCS	3A+
Murphy et al. [85]	Acquisition of a new strain of <i>P. aeruginosa</i> is associated with exacerbations of COPD	PCS	3A+

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

#### Recommendation:

- 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 resistance, tolerability, cost and potential compliance. Amoxicillin-clavulanic acid 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  $\beta$ -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 3 of admission if the patient is clinically stable [A3].

Oral gemifloxacin and levofloxacin (750 mg/24 h) over 5 days may be used to effectively treat AECOPD patients that require hospitalization [474,475]. This information comes from two randomized clinical trials that compare these two quinolones with standard treatments (10 days) in hospitalized and non-hospitalized patients with AECB.

A meta-analysis of randomized controlled-trials (including six studies on hospitalized AECOPD patients), comparing what they called first-line (amoxicillin, ampicillin, trimethoprim-sulphamethoxazol) with second-line antibiotics (amoxicillin-clavulanic acid, macrolides, second- or third-generation cephalosporins) for AECOPD, showed that first-line antibiotics were associated with lower treatment success compared with second-line antibiotics (mainly macrolides and amoxicillin-clavulanate; OR., 0.51) [476]

	Preferred	Alternative
Without risk factors for <i>P. aeruginosa</i>	Co-amoxiclav	Levofloxacin Moxifloxacin
+ Risk factors for <i>P. aeruginosa</i>	Ciprofloxacin <sup>a</sup>	Piperacillin/ tazobactam i.v.

<sup>a</sup>Levofloxacin 750 mg/24 h or 500 mg twice daily is an alternative.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Wilson et al. [474]	A randomized open label study comparing oral gemifloxacin for 5 days with ceftriaxone i.m./cefuroxime orally 10 days in hospitalized patients with AECB	RCT	2A+
Martinez et al. [475]	A randomized trial comparing 5 days of levofloxacin (750 mg/24 h) with amoxicillin-clavulanic acid for 10 days	RCT	2C+
Dimopoulos et al. [476]	A meta-analysis comparing first-line with second-line antibiotics in AECOPD	SR	1A+

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

#### Recommendation:

- 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.

In one study colonization by non-fermenting GNB, mainly *Pseudomonas aeruginosa*, was significantly associated with non-invasive mechanical ventilation failure in patients with AECOPD admitted to the ICU [477].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Ferrer et al. [477]	To study microbiological determinants associated with NIMV failure in AECOP	PCS	3A+

### Exacerbations of bronchiectasis

General recommendations for exacerbations of bronchiectasis.

#### Recommendation:

- 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 carried out 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 section What are the risk factors for *P. aeruginosa*? above).
- 5 Empirical antibiotics should be adjusted or modified according to sputum culture results [A3].

New information. Recommendation not changed.

The combination of ciprofloxacin and inhaled tobramycin may improve microbiological and clinical outcome. However, in 50% of patients treated with inhaled tobramycin wheezing was observed [478].

Prolonged antibiotic therapy has shown small benefit in modifying the outcome of purulent bronchiectasis [479] [B2].

What antibiotics are recommended for exacerbations of bronchiectasis? [C4]. The risk of *P. aeruginosa* infection should be considered. No validated risk factors are available; however, risk appears to be related to recent antibiotic therapy or hospitalization, serious disease or prior isolation of *Pseudomonas* species [89]

#### Recommendation:

	Oral treatment	Parenteral treatment
No risk of <i>Pseudomonas</i> spp.		Amoxicillin-clavulanate Moxifloxacin Levofloxacin
Risk of <i>Pseudomonas</i> spp. <sup>a</sup>	Ciprofloxacin <sup>b</sup>	Ceftazidime, or carbapenem, or piperacillin-tazobactam

<sup>a</sup>Use the same criteria mentioned for chronic obstructive pulmonary disease exacerbation.  
<sup>b</sup>Levofloxacin 750 mg/24 h or 500 mg twice daily is an alternative.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence level
Evans et al. [479]	To identify the role of prolonged antibiotic therapy in modifying the outcome of purulent bronchiectasis	MA	1B-
Bilton et al. [478]	To study the effect of adding inhaled tobramycin solution to oral ciprofloxacin for the treatment of acute exacerbations of non-CF bronchiectasis in patients with <i>P. aeruginosa</i> infection	RCT	2A-
Angrill et al. [89]	To investigate the incidence, diagnostic yield of non-invasive and bronchoscopic techniques, and risk factors for airway colonization in patients with bronchiectasis in a stable clinical situation	PCS	3B+

### Prevention

#### Prevention by methods other than vaccination

Does oral immunization with bacterial extracts prevent LRTI?

**Recommendation:** 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 [480–483]. Recommendation not changed.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study, CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Cogo et al. [480]	Prophylaxis of AE of COPD by a sublingual vaccine	CCS	3C+
Foxwell et al. [481]	Cochrane: <i>H. influenzae</i> oral vaccine for the prevention of AE of COPD	MA	1A+
Steurer-Stey et al. [482]	BronchVaxom: meta-analysis	MA	1B-
Tricarico et al. [483]	Oral bacterial (mechanical lysis) sublingual	RCT	2A+

What is the role of prophylactic antibiotic therapy in chronic bronchitis or COPD?

**Recommendation:** In patients with CB or COPD, oral or parenteral antibiotics should not be given for prevention [A1].

New information [484,485]. The PULSE study investigated whether a pulsed therapy with moxifloxacin every 8 weeks for 5 days over a 6-month period was able to prolong the time to the next exacerbation in COPD patients in comparison to placebo. The study was negative, although there was some trend that patients with purulent sputum showed a prolongation of the time to the next acute exacerbation [487].

Recommendation not changed.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Black et al. [484]	Prophylactic antibiotics for chronic bronchitis	MA	1A+
Smucny et al. [485]	Antibiotics for acute bronchitis	MA	1A-
Sethi et al. [487]	Proof-of-concept study evaluates whether intermittent pulsed moxifloxacin treatment (5 days/8 weeks) could reduce the frequency of these exacerbations	RCT	2A-

What is the role of prophylactic antibiotic therapy in patients with COPD or bronchiectasis? (a) COPD

**Recommendation:** The use of nebulized antibiotics or intermittent long-term macrolide therapy is not recommended in COPD patients in general [C4].

The use of nebulized antibiotics for the prevention of LRTI has only been studied in small groups of patients with COPD.

One randomized clinical trial has investigated the use of erythromycin (2 × 250 mg/day) over 12 months in COPD patients, with the aim of reducing moderate to severe exacerbations in these patients [486]. In total, 109 outpatients have been included in the trial: 69 (63%) male; 52 (48%) current smokers; mean (SD) age, 67.2 (8.6) years; FEV<sub>1</sub>, 1.32 (0.53) L; FEV<sub>1</sub>% predicted, 50 (18%). Thirty-eight (35%) of the patients had three or more exacerbations in the year before recruitment, with no differences between treatment groups. There was a total of 206 moderate to severe exacerbations; 125 occurred in the placebo arm. Ten in the placebo group and nine in the macrolide group withdrew. Generalized linear modelling showed that the rate ratio for exacerbations for the macrolide-treated patients compared with placebo-treated patients was 0.648 (95% confidence interval, 0.489, 0.859; *p* 0.003) and that these patients had shorter-duration exacerbations compared with those on placebo.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Seemungal et al. [486]	To study the efficacy of adding 2 × 250 mg erythromycin to the existing treatment regimen in patients with COPD	RCT	2A+
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#### (b) Bronchiectasis—nebulized antibiotics

**Recommendation:** There is not enough evidence to recommend the use of nebulized antibiotics (tobramycin) in non-CF-bronchiectasis [C2].

Nebulized tobramycin has been used with some success in cystic fibrosis patients. In non-CF-bronchiectasis patients, only small studies have been done. One found no effect [488] and one [489] found a decrease of hospital admission and some clinical improvement. Clear evidence for a recommendation to use inhaled tobramycin could not be drawn from these studies.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review [C4].

Reference	Objective	Design	Evidence
Drobnic et al. [488]	To study aerosolised tobramycin vs. placebo in non-CF bronchiectasis	RCT	2B-
Barker et al. [489]	To study aerosolised tobramycin vs. placebo in non-CF bronchiectasis	RCT	2B+

#### (c) Bronchiectasis—macrolides

**Recommendation:** There is not enough evidence to recommend the use of intermittent long-term macrolide therapy in non-CF-bronchiectasis in general [C2].

Use of intermittent macrolide therapy has been successful in patients with CF and patients following lung transplantation. The number of studies investigating non-CF-bronchiectasis patients is low. Besides some letters, case reports and very small studies [490], one retrospective study has been published. This study investigated prophylaxis with 3 × azithromycin/week in bronchiectasis patients. A reduction of acute exacerbations of 50% has been observed, as well as an increase of FEV<sub>1</sub> [491].



## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Cymbala <i>et al.</i> [490]	To study the efficacy of the addition of 6-months' twice-weekly azithromycin to the existing treatment regimen in patients with bronchiectasis	RCT	2A+
Anwar <i>et al.</i> [491]	To study the effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis	RCS	4C+

*Does antibiotic treatment of upper respiratory tract infections prevent LRTI?*

**Recommendation:** 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?*

**Recommendation:** 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?*

**Recommendation:** Physiotherapy should not be used as a preventive measure against LRTI [C4].

No new information. Recommendation not changed.

*Do antiviral substances prevent influenza virus infection?*

**Recommendation:** 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 [492]. Recommendation not changed.

## Evidence Table

Reference	Objective	Design	Evidence
Nordstrom <i>et al.</i> [492]	Oseltamivir prevents pneumonia, and decreases the use of antibiotics in patients with ILD	CCS	3B+

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

*Are oral mucolytics useful for the prevention of LRTI?*

**Recommendation:**

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].

Although it has been shown that oral mucolytics prevent acute exacerbations in patients with chronic bronchitis (IA+), it has not been shown that these substances prevent infection in the general population. However, there is some evidence that individuals 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, may benefit from a prescription of oral mucolytics through the winter months (IA+).

A third systematic review in a row has shown at least some effect of oral mucolytics in selected patients (severe COPD, frequent exacerbations, no ICS) [493].

## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Poole <i>et al.</i> [493]	Mucolytics for CB or COPD	MA	IA+

*Is there evidence that homeopathic substances prevent LRTI?*

**Recommendation:** Homeopathic substances should not be used as a preventive measure against LRTI [C4].

New information [494–496]. Recommendation not changed.

## Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Douglas et al. [494]	Vitamin C against common cold	MA	IA–
Barrett et al. [495]	Ecchinacea for common cold	RCT	2A–
McElhane et al. [496]	Extract of the roots of North American ginseng ( <i>Panax quinquefolium</i> )	RCT	2A+
Heimer et al. [497]	Vitamin C to prevent common cold	MA	1B–

#### Oral care in nursing homes.

**Recommendation:** 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].

Since the last version of these recommendations one meta-analysis and two intervention trials have investigated the question of intensified oral care in nursing home patients in relation to the prevention of LRTI or pneumonia.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Sjogren et al. [498]	A systematic review of the preventive effect of oral hygiene on pneumonia and respiratory tract infection in elderly people in hospitals and nursing homes	MA	1B+
Awano et al. [499]	To study the risk of death from pneumonia in relation to dental status	CCS	4C+
Bassim et al. [500]	To study the risk of mortality from pneumonia with oral hygiene care	CCS	3B+

*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 LRTI/CAP in COPD patients.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS,

retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review

Reference	Objective	Design	Evidence
Singh et al. [501]	Randomized controlled trials of any inhaled corticosteroid vs. a control treatment for COPD, with at least 24 weeks of follow-up and reporting of pneumonia as an adverse event were included	MA	IA+
Almirall et al. [502]	1336 patients with confirmed CAP were matched to control subjects by age, sex and primary centre over 1 year. Multivariable analysis confirmed inhalation therapy (particularly containing steroids and using plastic pear-spacers) as independent risk factors	CCS	4B+
Ernst et al. [503]	To study the effect of inhaled corticosteroids on pneumonia hospitalization	CCS	4B+
Drummond et al. [504]	To study the effect of inhaled corticosteroids on pneumonia mortality	MA	IA+
Sin et al. [505]	Pooled patient data from seven clinical trials of inhaled budesonide for the risk of pneumonia	MA	IA–

*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 than for ACE inhibitors.

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review.

Reference	Objective	Design	Evidence
Mortensen et al. [506]	Effect of current statin use and ACE inhibitor use on 30-day mortality of patients hospitalized for pneumonia	CCS	4B+
Chalmers et al. [507]	To study effects of statin use on mortality in those admitted to hospital with pneumonia	CCS	3B+
Dublin et al. [508]	Case-control study of statin use in pneumonia	CCS	4B–
Schlienger et al. [509]	Current statin users had a significantly reduced risk of fatal pneumonia	CCS	B4+
Thomsen et al. [510]	To study mortality in pneumonia in current statin users	CCS	4B+
Tleyjeh et al. [511]	To study statin use to prevent infection	SR	IA+

#### Recommendations for influenza vaccination

*Should influenza vaccine be used to prevent LRTI?*

#### Recommendation:

I Influenza vaccine should be given yearly to persons at increased risk of complications due to influenza [A2].

Vaccination should be given to 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 [6].

- 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]

In the elderly (>65 years of age) and in high-risk adults, irrespective of age, new studies have confirmed that seasonal influenza vaccination is effective in prevention of severe complications or death due to influenza [512–515]. As most of these results are based on non-controlled studies, they may result in either a too pessimistic or too optimistic view of the effectiveness of vaccination. The latter, based on 'healthy user biases', has been shown in several recent studies [515–518].

A recent Cochrane analysis was unable to reach clear conclusions about the effects of the influenza vaccine in the elderly [519], but it must be emphasized that a lack of evidence does not equal a lack of effectiveness. So far, there is unfortunately only one randomized controlled study of high quality [520]. This study clearly demonstrated that the vaccine was effective in prevention of clinical and laboratory verified influenza in the elderly, but was not powered to detect effects on complications. However, based on that study it is reasonable to assume that the vaccine will also prevent severe influenza and its complications, which is in accordance with the findings of a large majority of well-performed observational studies.

The specific age-limit of  $\geq 65$  years of age for recommendation of general seasonal influenza vaccination used in these guidelines is based on the fact that most trials have used this cut-off for the inclusion of patients and/or the analysis of the results. In some countries general vaccination is recommended also for some age groups below 65 years (e.g. in the USA, where vaccination is recommended for all persons aged 50–64 years because persons in this age group have an increased prevalence of high-risk conditions and low vaccination rates) [521].

Yearly vaccinations with the seasonal influenza vaccine do not lead to a decreasing immune response or protection, or

to more frequent effects than those seen after primary vaccination. Two new studies have confirmed that the inactivated injectable influenza vaccine is superior to the live attenuated vaccine in healthy adults [522,523]. However, although the seasonal influenza vaccine prevents respiratory illnesses in healthy adults [523,524], a revision of the Cochrane analysis by Demicheli *et al.* [525] indicates that vaccination is of only limited clinical value in this group of patients.

Systematic reviews indicate that vaccination of health care personnel against influenza may reduce influenza-like illness and all-cause mortality of elderly people in long-term hospitals, but have not demonstrated an effect on specific outcomes, such as laboratory-proven influenza, pneumonia or deaths from pneumonia [526,527].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review.

Reference	Objective	Study design	Evidence level
Demicheli <i>et al.</i> [525]	To study the effectiveness of influenza vaccination in persons 14–64 years of age	SR	1A+
Hak <i>et al.</i> [512]	To study the effectiveness of influenza vaccination in adult and elderly high-risk persons	CCS	4A+
Hak <i>et al.</i> [513] [2]	To study the effectiveness of influenza vaccination in adults 18–64 with COPD	CCS	4A+
Jackson <i>et al.</i> [516]	To study the effectiveness of influenza vaccination in elderly persons	RCS	4A+
Thomas <i>et al.</i> [526]	To study the effectiveness of influenza vaccination of health-care workers in order to protect elderly persons	SR	1A–
Squarcione <i>et al.</i> [528]	To study the immunogenicity and reactogenicity of inactivated influenza vaccine in older persons	RCT	2C–
Wang <i>et al.</i> [522]	To study live attenuated vs. inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel	PCS	3B+
Monto <i>et al.</i> [523]	Comparative efficacy of inactivated and live attenuated influenza vaccines in healthy adults	RCT	2A+
Nichol <i>et al.</i> [524]	To study the effectiveness of influenza vaccination in prevention of influenza-like illness	PCS	3B+
Schembri <i>et al.</i> [514]	To study the effectiveness of influenza vaccination in prevention of all-cause mortality in elderly persons	RCS	4A+
Örtqvist <i>et al.</i> [515]	To study the effectiveness of influenza vaccination in prevention of all-cause mortality in elderly persons	PCS	3A+
Eurich <i>et al.</i> [517]	To study the effectiveness of influenza vaccination in prevention of all-cause mortality in elderly persons	PCS	3A+
Jackson <i>et al.</i> [518]	To study the effectiveness of influenza vaccination in prevention of community-acquired pneumonia in immunocompetent elderly people	CCS	4A+
Jefferson <i>et al.</i> [519]	To study vaccines for preventing influenza in the elderly	SR	1B–
Thomas <i>et al.</i> [527]	To study the effect of influenza vaccination for healthcare workers who work with the elderly	SR	1B–

### Recommendations for pneumococcal vaccination

*Should pneumococcal vaccine be used to prevent LRTI?*

#### Recommendation:

- 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 of 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.

The immunogenicity of the 23-valent polysaccharide pneumococcal vaccine (PPV) is generally good, but may be poor in some elderly patients or in persons with some underlying illnesses (e.g. bronchiectasis) [529]. It is also important to stress that the PPV includes 23 antigens and that a person can develop a pneumococcal disease from one of these serotypes, despite responding to all the others [530]. Previously, there have been conflicting data concerning whether a pneumococcal conjugate vaccine (PCV) could result in a superior immune response in elderly patients or high-risk adults, compared with PPV [531], but a couple of recent studies do indicate that this may be the case [532,533]. The drawbacks of PCV, however, are the limited number of serotypes, the much higher price, and the lack of data on efficacy (although a large RCT is underway).

Vaccination of children with PCV may be of benefit also for adults. Since the start of vaccination of children with PCV in the USA in 2000 a marked reduction of IPD has been noted both in the vaccinated cohorts and in adults [534,535]. This 'herd immunity' effect has been most marked in the age groups of parents (20–39 years of age) and grandparents (above 65 years of age). Concerning other outcomes, the herd effect is less clear, with one study indicating a decrease of all-cause pneumonia and pneumococcal pneumonia in

adults 18–39 years of age [536], while another showed no impact at all for all-cause pneumonia in adults [537].

The efficacy of PPV in adults, including the elderly, has been evaluated in eight meta-analyses/systematic reviews (MA/SR) of randomized controlled trials (RCTs). The three most recent reviews have also included a systematic review of observational studies of invasive pneumococcal disease (IPD) [538–541]. During the last 2 years, one double-blind randomized controlled trial and some other studies on the effectiveness of PPV have been published [542–550].

The MA/SRs of RCTs have shown strong evidence of PPV efficacy in prevention of invasive pneumococcal disease (IPD) in healthy adults, including the elderly (40–75% protective efficacy), while the effect against IPD may be somewhat poorer in persons with chronic illnesses. The estimates of protection against IPD from SRs of observational studies have been consistent, homogenous and compatible with those of RCTs [538–541]. Reports of significant reductions in the incidence of IPD in the elderly after the introduction of large-scale vaccination programmes from two European countries support the effectiveness of the vaccine against IPD [551,552].

There is very limited evidence that PPV prevents all-cause pneumonia in the elderly or in other risk groups. However, a recent double-blind randomized controlled trial among about 1000 nursing home residents in Japan demonstrated that PPV was associated with a reduction of the incidence of all-cause pneumonia by 45% and of pneumococcal pneumonia by 64% [546]. There was also a significant higher death rate among persons with pneumococcal pneumonia in the placebo group, 35% (13/37) vs. 0% (0/14). This study supports earlier findings from recent cohort studies indicating that PPV is associated with a reduction of pneumonia overall, pneumococcal pneumonia, hospitalization for pneumonia and death due to pneumonia [544,545,547,553,554]. In contrast, some other cohort studies have found no protection against all-cause pneumonia or hospitalization for pneumonia [543,550].

In an open RCT, performed in adults with COPD, a high degree of protection against CAP due to *S. pneumoniae* or unknown aetiology was seen in persons <65 years of age, and especially in those with severe functional obstruction ( $FEV_1 < 40\%$ ) [542]. In contrast, pneumococcal vaccination did not alter significantly the risk of overall CAP in a cohort study of older adults with chronic respiratory diseases [548].

In European studies, vaccination with PPV of the elderly has not been cost-saving, but shown moderate to good cost-effectiveness in preventing hospital admission for IPD [555,556]. The most recent study [556] indicated that pneumococcal vaccination would be cost neutral if it was 75–89% efficacious against IPD or 28–38% against pneumococcal pneumonia in

the elderly. If the vaccine efficacy against IPD was 50% the net cost for society would be £2500 per year of life saved. Using data on the effect of herd immunity from the USA, it has been estimated that it would be cost-effective from an adult point of view to vaccinate children in the UK with four doses of the seven-valent conjugate vaccine [557].

The safety and immunogenicity of one revaccination with pneumococcal vaccine has been confirmed by several studies [558–560]. In a large randomized controlled trial patients who previously had received one dose of PPV were randomized to receive PPV or PCV, in four different dosages [558]. Local side-effects were common, but usually mild. The frequency of local reactions in the PCV group depended on the dose given, and in the highest dosage group the risk of a reaction was comparable to that of PPV. In a prospective cohort study of 61 elderly persons (median age 75 years) revaccinated on average 5.3 years after the primary vaccination, significant increases of the geometric mean antibody concentration and geometric mean antibody fold increase were seen, although to lower levels than after primary vaccination [559]. Thirty-six of 61 (59%) of patients responded with a fold increase >2, to two or more of six serotypes. Early revaccination may lead to a short-lived antibody rise, which could be due to an immunological suppression or tolerance [532]. However, this suppressive effect seems to wane after some years and in studies where revaccination has been performed after 5 years or more persons have responded well [559,560].

#### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review.

Reference	Objective	Study design	Evidence level
Van Kessel <i>et al.</i> [529]	To study immunogenicity of PPV in patients with bronchiectasis	PCS	3C–
Abraham-Van Parijs <i>et al.</i> [531]	To compare immunogenicity of PPV and PCV in healthy and high-risk adults	SR	1B–
Kyaw <i>et al.</i> [534]	To study the effectiveness of reducing IPD in adults by vaccination of children with conjugate pneumococcal vaccine	RCS	4C+
Whitney <i>et al.</i> [535]	To study the effectiveness of reducing IPD in adults by vaccination of children with conjugate pneumococcal vaccine	RCS	4C+
Melegaro and Edmunds [538]	To study the efficacy of PPV in adults above 50 years of age	SR	1A–
Dear <i>et al.</i> [539]	To study the efficacy of PPV in adults	SR	1A–
Conaty <i>et al.</i> [540]	To study the efficacy of PPV in adults	SR	1A–

Alfageme <i>et al.</i> [542]	To study the efficacy of PPV in adults with COPD	RCT	2C+
Jackson <i>et al.</i> [543]	To study the efficacy of PPV in adults above 65 years of age	RCS	4B+
Christenson <i>et al.</i> [544]	To study the efficacy of PPV in adults above 65 years of age	PCS	3B+
Vila-Córcoles <i>et al.</i> [545]	To study the efficacy of PPV in adults above 65 years of age	PCS	3B+
Fisman <i>et al.</i> [553]	To study the efficacy of PPV in adults	RCS	4C+
Mykietiuk <i>et al.</i> [554]	To study the efficacy of PPV in adults	PCS	3C+
Melegaro <i>et al.</i> [555]	To study cost-effectiveness of PPV in elderly persons	RCS	5B+
Mangtani <i>et al.</i> [556]	To study cost-effectiveness of PPV in elderly persons	RCS	5B+
McIntosh <i>et al.</i> [557]	To study cost-effectiveness in adults after vaccination of children with PCV	RCS	5B+
Jackson <i>et al.</i> [558]	To compare safety of PPV and PCV in elderly persons	RCT	2A+
Törling <i>et al.</i> [559]	To study the immune response to revaccination with PPV in elderly persons	PCS	3A+
Sisk [26]	To study cost-effectiveness of PPV in adults 50–54 years of age	RCS	5B+
Andrews [27]	To study the efficacy of PPV in adults above 65 years of age	PCS	4C+
Pepper [28]	To study cost-effectiveness of PPV in healthy adults	RCS	5B+
Ortqvist <i>et al.</i> [530]	To study response to specific serotypes causing failure of 23-valent pneumococcal polysaccharide vaccine in the elderly	CCS	4A+
Musher <i>et al.</i> [532]	To study the initial and subsequent response to pneumococcal polysaccharide and protein-conjugate vaccines administered sequentially to adults who have recovered from pneumococcal pneumonia	PCS	3B+
de Roux <i>et al.</i> [533]	To compare pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults	RCT	2B+
Grijalva <i>et al.</i> [536]	To study pneumonia admissions after routine childhood immunization with pneumococcal conjugate vaccine in the USA	RCS	4B+
Nelson <i>et al.</i> [537]	To study impact of the introduction of pneumococcal conjugate vaccine on rates of community-acquired pneumonia in children and adults	RCS	4A+
Moberley <i>et al.</i> [541]	Systematic review of vaccines for preventing pneumococcal infection in adults	SR	1A+
Maruyama <i>et al.</i> [546]	To study the efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents	RCT	2A+
Christenson <i>et al.</i> [547]	To study the effect of influenza and pneumococcal vaccines in elderly people	PCS	3C+
Ochoa-Gondar <i>et al.</i> [548]	To study the effectiveness of pneumococcal vaccination in older adults with chronic respiratory diseases	PCS	3B–
Lee <i>et al.</i> [549]	To study the impact of pneumococcal vaccination on pneumonia rates in adult patients with COPD and asthma	RCS	4B+
Skull <i>et al.</i> [550]	To study whether influenza and/or pneumococcal vaccine prevents hospitalization because of community-acquired pneumonia in the elderly	CCS	4B–
Johnstone <i>et al.</i> [561]	To study the effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia	PCS	3B+
Waites <i>et al.</i> [560]	To study the effects of revaccination of adults with spinal cord injury using the 23-valent pneumococcal polysaccharide vaccine	PCS	3A+



### Recommendations for implementation.

**Recommendation:** Active interventions should be used to enhance vaccination with either, or both, of the vaccines and is effective and needed to in order to achieve an adequate vaccination coverage of the targeted population [A1].

New studies have confirmed that different types of interventions (e.g. patient reminders or standing orders) are effective for increasing vaccination of the targeted population against influenza and pneumococcal disease [562–565].

### Evidence Table

MA, meta-analysis (or systematic review); RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; CCS, case-control study; CSS, cross-sectional study; SR, systematic review.

Reference	Objective	Study design	Evidence level
Dexter et al. [562]	To study the effectiveness of different methods to increase vaccine coverage in adults eligible for vaccination	RCT	2C+
Jacobson et al. [563]	To study the effectiveness of different methods to increase vaccine coverage in adults of all age groups	SR	1A+
de Hart et al. [564]	To study the effectiveness of different methods to increase vaccine coverage in elderly persons	PCS	3C+
Jha et al. [565]	To study performance measures, vaccinations and pneumonia rates among high-risk patients in Veterans Administration health care	RCS	4C+

## Appendix I

### Evidence grades (~hierarchy of methods)

1. = Systematic reviews and meta-analyses (of study types under grade 2 or 3)
2. = Randomized trials
3. = Prospective cohort
4. = Case-control, cross-sectional, retrospective cohort
5. = Case reports
6. = Expert opinion, consensus

Suffix for evidence grades 1–6A = low risk of biased results (flaws very unlikely for both blinding and follow-up)

B = moderate risk of biased results (flaws unlikely for both blinding and follow-up)

C = high risk of biased results (flaws likely for either or both blinding and follow-up)

Suffix for evidence grades 1A–6C.+ = determinant-outcome relation of interest clearly established

i.e. the numerical results from the study unequivocally support a positive answer to the research question

– = determinant-outcome relation of interest clearly not established

i.e. the numerical results from the study are unequivocally not supportive of a positive answer to the research question

? = determinant-outcome relation of interest unclear

## Appendix 2

### Recommendation grading

#### Grades

A = Consistent evidence ->Clear outcome

B = Inconsistent evidence ->Unclear outcome

C = Insufficient evidence ->Consensus

Suffix for recommendation grades A–C

For studies of diagnosis and treatment (including prevention and harm)

1. = Systematic review (SR) or meta-analysis (MA) of RCTs
2. = 1 RCT or more (>1: no SR or MA yet)
3. = 1 cohort study or more (>1: no SR or MA yet)
4. = Else

For studies of prognosis and aetiology

1. = SR or MA of cohort studies
2. = 1 cohort study or more (>1: no SR or MA yet)
3. = Else

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