

## **APPENDIX 1: INTRODUCTION, DETAILED METHODS AND DEFINITIONS**

### ***Introduction***

Lower respiratory tract infections (LRTI) are an important problem. They occur frequently, are associated with significant morbidity and mortality, present in a variety of healthcare settings and impose a considerable cost on European healthcare services. Guidelines for their management may therefore be useful. In 1998, the European Respiratory Society (ERS) published such guidelines [1]. Since that time, the evidence on which the guidelines were based has increased and the methods for guideline development have been refined. It is against this background that these new guidelines have been developed.

### ***What is the objective of the guidelines?***

The objective is to summarise the best available evidence from clinical research and provide useful clinical recommendations. By providing clinicians with information on the best available evidence with respect to risk factors for and the occurrence, diagnosis, prognosis and management of community-acquired LRTI (CA-LRTI), we aim to maximise the potential benefits for patients with CA-LRTI.

### ***What are the reasons for the development of the guidelines?***

There are at least three reasons for the development of the guidelines. First of all, in recent years the number of relevant papers on CA-LRTI has grown rapidly; from 1995–2000, at least 805 relevant papers per year can be found on PubMed, whilst from 2000–2003, at least 1,497 papers per year can be found. It is therefore impossible for anyone to get a comprehensive overview of the research on CA-LRTI or to keep clinical management in step with the large amount of relevant clinical evidence. Secondly, attempts to keep up to date by reading new clinical research findings frequently tend to be based on haphazard selection from all the relevant new publications. Moreover, it is known that positive research results are more likely to be recognised and remembered. Thirdly, this mechanism is likely to hamper the synthesis of clinical data because positive results are not necessarily valid. For example, in absence of a control group, the natural course and regression to the mean may give rise to biased result from routine clinical follow-up, while incomplete follow-up and lack of blinding of assessments will further reduce the validity of such data. It must be noted that adequately controlled and blinded studies are not always conceivable.

### ***What do the guidelines cover?***

The guidelines provide recommendations for important LRTI management questions (see Definitions section), which arise in an adult in the community and cover management both outside and inside the hospital and prevention.

### ***What don't the guidelines cover?***

They do not cover: LRTI in children; cystic fibrosis; LRTI in the immunocompromised; LRTI that might be considered to be nosocomial in origin; LRTI that are expected to be the terminal event in some other chronic disease process. For conditions in which the management of infection is only one part of the management of the acute condition (*e.g.* exacerbations of chronic obstructive pulmonary disease (COPD) or bronchiectasis), the guidelines will only deal with aspects related to the infection.

### ***Who are the guidelines intended for?***

All healthcare personnel involved in making management decisions for patients with LRTI in the community and the hospital; healthcare teachers and trainers; healthcare personnel in training; and healthcare planners.

### ***Who has developed the guidelines?***

They have been written by a committee of experts in respiratory infections, covering the disciplines of general practice, hospital respiratory medicine, microbiology, infectious diseases and intensive care, together with an expert in guideline methodology. The guidelines have been sponsored by the ERS, in collaboration with the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). They have been peer reviewed by R. Finch (personal communication; Dept of Microbiology and Infectious Diseases, Clinical Sciences Building, Nottingham, UK) and M. Struelens (personal communication; Dept of Microbiology, Universite Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium).

### ***How were the guidelines developed?***

Guidelines aim to summarise the best available evidence from clinical research [2, 3]. In clinical research, however, heterogeneity is seen in the research question, validity of the design and conduct of the study. Consequently, research results are not necessarily consistent. When summarising the best available evidence one must take this heterogeneity and lack of consistency into account. In order to avoid/reduce the influence of poor design and conduct of research on the production of the guidelines, we took an explicit approach to summing up the clinical evidence. We performed a systematic literature search in order to retrieve relevant publications, critically appraised and rated the pertinent clinical evidence, summarised these ratings in levels of evidence, and translated the best available evidence into graded clinical recommendations. We used the methods for appraisal and summarising evidence that are described elsewhere [3].

### ***How were relevant publications retrieved?***

We developed a systematic strategy for searching the clinical evidence available on PubMed, the online medical bibliography of the National Library of Medicine. We searched for English language publications, published between 1 January, 1966 and 31 December, 2002. The selection and critical appraisal of the evidence, summarisation of the evidence and the production of the written guideline text of was planned thereafter.

As LRTI is not a clearly defined medical entity, a bibliographical index or thesaurus term is lacking, so a search filter for LRTI had to be developed. A list of relevant medical terms and keywords were chosen from textbooks and appropriate publications. These were localised in the PubMed index (tagged words in title, abstract, medical subject headings, publication types of PubMed records) and the PubMed thesaurus (hierarchical systematic index of keywords). The list of keywords was combined using Boolean operators (AND, OR), resulting in a comprehensive draft search filter. By adding the Boolean operator NOT with major mesh terms for irrelevant medical subjects (for example, relating to paediatrics, nosocomial infections, cystic fibrosis, immunocompromised and terminally ill) to the draft search filter, it was hoped that the majority of such publications would be excluded. Most of

the letters, editorials, comments, conference abstracts, animal studies and *in vitro* studies were excluded in a similar way.

Subsequently, we combined the resulting search filter for LRTI with online available search filters for the retrieval of guidelines, consensus statements, systematic reviews, and original diagnostic, prognostic, therapeutic and aetiological studies (<http://www.ncbi.nlm.nih.gov:80/entrez/query/static/clinical.html> and <http://www.gimbe.org/Praticare-EBM/PubMed-Strategies.doc>). Finally, in an iterative process, the resulting search filter was tested, adapted and refined, in order to include a set of “criterion” citations obtained from field experts.

With the final search filter (see below), we retrieved 26,203 titles (from the period spanning 1966–2002) from PubMed, and loaded them into an electronic database. In total, 6,843 (26%) were available as (free) full text electronic publications.

The following PubMed search filter was used for the ERS LRTI guidelines:

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((("Bronchitis"[mh] OR "Pneumonia"[mh] OR "Bronchiectasis"[mh] OR "Whooping Cough"[mh] OR "Influenza"[mh] OR "Legionellosis"[mh] OR "Common Cold"[mh] OR "Cough"[mh] OR "Sputum"[mh] OR "Community-Acquired Infections"[mh]) AND "English"[LA]) NOT ("Otorhinolaryngologic Diseases"[majr] OR "Neoplasms"[majr] OR "HIV Infections"[majr] OR "Cytotoxins"[majr] OR "Cardiovascular Diseases"[majr] OR "skin tests"[majr] OR "Perioperative Care"[majr] OR "Anti-Asthmatic Agents"[majr] OR "tuberculosis"[majr] OR "Postoperative Complications"[majr] OR "antioxidants"[majr] OR "transplantation"[majr] OR letter [pt] OR editorial [pt] OR comment [pt] OR in vitro [mh] OR ("animal"[mh] NOT ("human"[mh] AND "animal"[mh]))) AND ((("guideline"[pt] OR "practice guideline" [pt] OR "health planning guidelines" [mh] OR "consensus development conference" [pt] OR "consensus development conference, nih" [pt] OR "consensus development conferences" [mh] OR "consensus development conferences, nih" [mh] OR "guidelines" [mh] OR "practice guidelines" [mh] OR (consensus [ti] AND statement [ti])) OR ("meta-analysis"[pt] OR "meta-anal*" [tw] OR "metaanal*" [tw] OR "quantitativ* review*" [tw] OR "quantitative* overview*" [tw] OR "systematic* review*" [tw] OR "systematic* overview*" [tw] OR "methodologic* review*" [tw] OR "methodologic* overview*" [tw] OR ("review"[pt] AND "medline"[tw])) OR (cohort studies [mh] OR risk [mh] OR (odds [tw] AND ratio* [tw] OR case control* [tw] OR case-control studies [mh] OR (relative [tw] AND risk [tw])) OR (incidence [mh] OR mortality [mh] OR follow-up studies [mh] OR mortality [sh] OR prognos* [tw] OR predict* [tw] OR course [tw]) OR (sensitivity and specificity [mh] OR sensitivity [tw] OR diagnosis [sh] OR diagnostic use [sh] OR specificity [tw]) OR (randomized controlled trial [pt] OR drug therapy [sh] OR therapeutic use [sh:noexp] OR random* [tw])) Field: All Fields, Limits: Publication Date to 2003/01/01
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### ***How was relevant evidence selected?***

Papers were chosen for inclusion using a non-selective strategy, reducing the chance of reviewer or selection bias. For the selection of relevant citations, a pragmatic approach was taken. To handle the workload of selection from the large number of relevant titles initially retrieved by the search filter, the work was divided between the experts in the editorial team. To each expert, and irrespective of their speciality in the

field, about 3,500 retrieved citations were allocated for selection of publications for further use during guideline writing. The selection of potentially relevant publications was based on the following criteria. 1) Study population. Publications concerning adult patients in primary or secondary care with primary (*i.e.* non-comorbid) LRTI were considered for inclusion. Publications involving healthy control subjects or patients with postoperative and post-traumatic conditions, and those involving patients with LRTI related to a specific underlying disease or as a result of comorbidity (with the exception of COPD and bronchiectasis) were excluded. 2) Type of publication. Only full reports written in the English language on original patient data concerning patients with CA-LRTI were considered for inclusion. Conference abstracts, editorials, informal (expert) reviews, comments, letters, animal and *in vitro* studies (with the exception of pharmacokinetic studies) were excluded. 3) Type of study. The following study types were considered for inclusion: randomised trials, cohort studies, case control studies, cross-sectional studies, predictive modelling studies, systematic reviews and meta-analyses, plus single-subject studies and case reports for harm of treatment studies only.

When in doubt about the relevance based on the publication title, the experts read the (electronic) abstract. If they were still in doubt, they obtained and read the full paper (on-line paper or hard copy).

The workload of screening 3,500 citations proved to be equal to about 6 hours' work. In total, almost 10% of the titles retrieved from PubMed were selected (table 22), with a range of 4–13% among reviewers. After the exclusion of inaccurately selected publications, 2,264 titles (about 8%) remained (table 22). These citations were eligible for the critical appraisal of study methods. They were imported into an electronic citation management database.

Table 22 – Results of retrieval and selection of publications

Time period	Number of citations			
	Retrieved in PubMed		Selected by editors	
	Total	Per year	Total	Per year
Before 1 Jan. 1975	3893	433	133	27
1 Jan. 1975 to 31 Dec. 1979	2254	451	126	25
1 Jan. 1980 to 31 Dec. 1984	2664	533	167	33
1 Jan. 1985 to 31 Dec. 1989	3209	642	224	45
1 Jan. 1990 to 31 Dec. 1994	4057	811	376	75
1 Jan. 1995 to 31 Dec. 1999	5633	805	891	178
1 Jan. 2000 to 31 Dec. 2001	4490	1497	347	69
Total	26200	5172	2264	452

Jan.: January; Dec.: December.

Because a large amount of work had already been done, the selection procedure was not duplicated. As a result, some relevant papers known to the expert section editors could initially have been missed. Section editors were therefore allowed to add such papers, if they had been published before 31 December 2002. All papers, including those added in this way, were subsequently appraised for their quality of methods.

For some sections of the guidelines, information from the internet on morbidity figures and disease occurrence patterns was used. This was restricted to valuable information from generally acknowledged institutes, for which no related and up-to-date publication was available.

Sections of the guidelines were written by pairs of expert editors. Both had to agree on the inclusion of a publication as a reference in their section and on the outcome of the critical appraisal of study methods.

***How was the evidence appraised and rated?***

The appraisal was designed to discern valid from biased results and rate the studies according to the strength of evidence [4]. The strength of the evidence of clinical research is largely dependent on the validity of the study design (table 23). Furthermore, the presence of methodological flaws reduces the validity of clinical research, and thereby differentiates between studies with the same design with respect to their strength of evidence. Therefore, levels of evidence were defined based on the type of study design plus the bias in the conduct of studies. The only exception in this scheme is that randomisation can only be applied to clinical studies of a causal nature (*i.e.* preventive and therapeutic intervention studies) and not to those of a descriptive nature (*i.e.* diagnostic and prognostic studies).

Table 23 Strength of evidence based on hierarchy by study design

Strongest	Systematic reviews/meta-analyses Randomised trials* Cohort studies (comparison >1 group) Case control designs Patient series (1 group “cohort studies”)
Weakest	Case reports

\*: only applicable to therapeutic and preventive intervention research.

The editors of each section of the guidelines selected the publications that were relevant to their part. They used a checklist for the critical appraisal of each of the selected publications (fig. 2). This looked at the design type and the potential for bias and flaws with respect to completeness of data (*i.e.* loss to follow-up and missing data) and blinding of outcome assessments. Next, guided by a checklist for translating the critical appraisal results in levels of clinical evidence, the editors rated the strength of the evidence for each study (table 24). They then ranked studies for a particular clinical question in an evidence matrix, according to the levels of evidence and the magnitude of the reported outcome.

**STUDY OBJECTIVE**

- |  |   |
|--|---|
| <input type="checkbox"/> <b>Causal</b>                     | <input type="checkbox"/> <b>Descriptive</b> |
| <input type="checkbox"/> Aetiology (causes & risk factors) | <input type="checkbox"/> Diagnosis          |
| <input type="checkbox"/> Prevention                        | <input type="checkbox"/> Prognosis          |
| <input type="checkbox"/> Treatment                         |   |
| <input type="checkbox"/> Harm                              |   |

**TYPE OF DESIGN**

Original patient data:

- |   |  |
|---|--|
| <input type="checkbox"/> <b>Yes</b>                 | <input type="checkbox"/> <b>No</b>                       |
| <input type="checkbox"/> Randomised trial           | <input type="checkbox"/> Systematic review/Meta-analysis |
| <input type="checkbox"/> Prospective cohort study   | <input type="checkbox"/> Consensus statement             |
| <input type="checkbox"/> Retrospective cohort study | <input type="checkbox"/> Guidelines                      |
| <input type="checkbox"/> Case control study         | <input type="checkbox"/> Other .....                     |
| <input type="checkbox"/> Case report or case series |  |
| <input type="checkbox"/> Other .....                |  |

**MISSING DATA**

- |  | <b>Yes</b>               | <b>No</b>                | <b>Not known</b>         |
|--|--------------------------|--------------------------|--------------------------|
| a) > 10% data missing  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b) > 5% difference between groups for missing data                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c) Bias due to missing data  |                          |                          |                          |
| <input type="checkbox"/> Likely (only when yes for both items)       |                          |                          |                          |
| <input type="checkbox"/> Unlikely (all other combined responses)     |                          |                          |                          |
| <input type="checkbox"/> Very unlikely (only when no for both items) |                          |                          |                          |

**BLINDING**

- |  | <b>Yes</b>               | <b>No</b>                | <b>Not known</b>         |
|--|--------------------------|--------------------------|--------------------------|
| a) Blinding for determinant status*                                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| * <i>risk factor, diagnostic test, treatment, prognostic indicator</i> |                          |                          |                          |
| b) Blinding for outcome status**                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| ** <i>disease, gold standard, effect, course/endpoint</i>              |                          |                          |                          |
| c) Bias due to (lack of) blinding                                      |                          |                          |                          |
| <input type="checkbox"/> Likely (only when no for both items)          |                          |                          |                          |
| <input type="checkbox"/> Unlikely (all other combined responses)       |                          |                          |                          |
| <input type="checkbox"/> Very unlikely (only when yes for both items)  |                          |                          |                          |

**STUDY RESULTS**

- |  | <b>Yes</b>               | <b>No</b>                |
|--|--------------------------|--------------------------|
| ▪ Numerical results are clear                                      | <input type="checkbox"/> | <input type="checkbox"/> |
| ▪ Numerical results support a positive answer to clinical question | <input type="checkbox"/> | <input type="checkbox"/> |

Figure 2 Checklist for critical appraisal.

Table 24 Checklist for levels of evidence

Evidence levels (ranging from 1A+ TO 6C-)
<ul style="list-style-type: none"> <li>1 Systematic reviews &amp; meta-analyses (of study types under grade 2 or 3)</li> <li>2 Randomised trials</li> <li>3 Prospective cohort</li> <li>4 Case control, cross-sectional, retrospective cohort</li> <li>5 Case reports</li> <li>6 Expert opinion, consensus</li> </ul>
1st suffix
<ul style="list-style-type: none"> <li>A Low risk of biased results (flaws very unlikely for both blinding and follow-up)</li> <li>B Moderate risk of biased results (flaws unlikely for both blinding and follow-up)</li> <li>C High risk of biased results (flaws likely for either or both blinding and follow-up)</li> </ul>
2nd suffix
<ul style="list-style-type: none"> <li>+ Numerical results unequivocally support a positive answer to the research question (<i>i.e.</i> determinant–outcome relation of interest clearly established)</li> <li>– Numerical results unequivocally do not support a positive answer to the research question (<i>i.e.</i> determinant–outcome relation of interest not established)</li> <li>? Numerical results are unclear</li> </ul>

***How was the best clinical evidence translated into recommendations?***

The clinical recommendations sum up the best clinical evidence in meaningful clinical wording [3, 5].

The section authors formulated and graded the clinical recommendations for particular clinical questions. The grading is based on the information from the evidence matrix, and relates to the consistency of the evidence levels and the magnitude of reported outcomes [4]. Section authors used a checklist to translate evidence levels into grading for recommendations (table 25). The higher the grade of the recommendation, the higher the certainty about the strength of the recommendation, *i.e.* the more solid the evidence is, both in terms of validity and magnitude of outcome.

Table 25 Checklist for grading recommendations

Grades of recommendation (ranging from A1 to C4)
<ul style="list-style-type: none"> <li>A Consistent evidence: clear outcome</li> <li>B Inconsistent evidence: unclear outcome</li> <li>C Insufficient evidence: consensus</li> </ul>
Suffixes
For preventive and therapeutic intervention studies (including harm of intervention)
<ul style="list-style-type: none"> <li>1 SR or MA of RCTs</li> <li>2 1 RCT, or &gt;1 RCT but no SR or MA</li> <li>3 1 cohort study, or &gt;1 cohort study but no SR or MA</li> <li>4 Other</li> </ul>
For other studies
<ul style="list-style-type: none"> <li>1 SR or MA of cohort studies</li> <li>2 1 cohort study, or &gt;1 cohort study but no SR or MA</li> <li>3 Other</li> </ul>

SR: systematic review; MA: meta-analysis; RCT: randomised controlled trial.

### ***How were the antibiotic recommendations developed?***

The formulation of the antibiotic recommendations merits specific comment. As with other recommendations, these were based on evidence of both benefit and harm with respect to particular antibiotics. However, it was found that robust evidence to support individual recommendations was unavailable. This was partly because individual antibiotic studies do not capture all outcomes of importance in antibiotic management and also because there may be variation in the factors that might determine antibiotic recommendations in different geographical locations, which cannot be addressed by a single recommendation. Factors such as lack of statistical power to assess an outcome, selective patient recruitment, lack of subject blinding, lack of assessment of impact on the wider community (especially with regard to antimicrobial resistance) were common to most clinical studies of antibiotic effect. Such studies could therefore only be used to support a consensus view from the guideline authors.

The antibiotic recommendations should be interpreted with the above in mind and it should be accepted that an individual recommendation may not be suitable in every clinical setting. When an antibiotic is stated as “preferred” this should be taken to mean that in the view of the authors, based on available evidence, in usual everyday management, this antibiotic would have advantages over others. This is not to say that other antibiotics might not be effective and in some, usually less common, situations might even be preferred.

### ***Definitions***

These guidelines are to be used to guide the management of adults with LRTI. As will be seen in the following text, this diagnosis, and the other clinical syndromes within this grouping, can be difficult to make accurately. In the absence of agreed definitions of these syndromes, these guidelines are to be used when, in the opinion of a clinician, an LRTI syndrome is present. The following are put forward as definitions to guide the clinician, but it will be seen in the ensuing text that some of these labels will always be inaccurate. These definitions are pragmatic and based on a synthesis of available studies. They are primarily meant to be easy 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 both an umbrella term that includes all others but which can also be used for cases that cannot be classified into one of the other groups.

#### **Lower respiratory tract infection**

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

#### **Acute bronchitis**

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

### Influenza

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

### Suspected community-acquired pneumonia

An acute illness with cough and at least one of: new focal chest signs; fever > 4 days; dyspnoea/tachypnoea. No other obvious cause.

### Definite community-acquired pneumonia

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

An event in the natural course of the disease characterised by a worsening in 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 that is consistent with infection is present, the patient is considered to have community-acquired pneumonia (CAP).

### Acute exacerbation of bronchiectasis

In a patient with features that suggest bronchiectasis, an event in the natural course of the disease characterised by a worsening in 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 that is consistent with infection is present, the patient is considered to have CAP.

### *Why might the diagnosis be difficult to make?*

Respiratory tract infections (RTIs) are traditionally divided into those of the upper and lower parts of the respiratory tract. There are clinical as well as anatomical reasons for wishing to make this distinction. Upper respiratory tract infections (URTI) are usually viral in origin, not severe and self-limiting. LRTI are more often bacterial in origin, may be severe and might require specific medical intervention. LRTI are further divided into pathological and clinical syndromes, the most frequently used being: acute bronchitis (AB), influenza, CAP, acute exacerbation of COPD (AECOPD) and acute exacerbation of bronchiectasis (AEBX). These syndromes differ in frequency of bacterial and viral pathogens, illness severity and the need for specific management interventions. Unfortunately, this simple nomenclature ignores the difficulty of assignment of one of these labels to individual patients, especially outside hospital, where most patients are managed. Confounding factors to accurate diagnostic labelling are summarised in table 26.

Table 26 Factors which confound diagnostic labelling in lower respiratory tract infections

Symptoms and signs are not anatomical site specific
Symptoms and signs are not infection specific or infection syndrome specific
Inter-observer variability in identification of physical signs
Inter-observer variability in interpretation of symptom/sign complexes
Agreed definitions for diagnostic labels do not exist
Studies of the same topic use different definitions and therefore study different

populations
Inter-operator variability in the threshold for ordering chest radiographs
Inter-observer variation in chest radiograph reporting
CT studies show that CAP may be present when the chest radiograph is normal

CT: computed tomography; CAP: community-acquired pneumonia.

Micro-organisms (*e.g.* influenza virus) do not respect the barrier between the upper and lower respiratory tract, meaning LRTI and URTI may coincide or may be sequential. The symptoms and signs used to clinically separate these syndromes are few in number and specific neither to individual anatomic sites nor to diagnostic labels nor infective illness. Cough, for example, can occur with URTI and LRTI [6] and may be a feature of airway disease, interstitial lung disease, left ventricular failure and even a drug side-effect. These symptoms and signs are subject to inter-observer variability [7, 8]. Agreed definitions for these diagnostic labels have not been developed, which means that a patient with a given symptom/sign complex may be given a different diagnostic label by different physicians [9, 10]. In a study of RTIs identified simultaneously by 141 general practitioners (GPs), the proportion of LRTI ranged from 6% to 61% between GPs, a variation that cannot be explained by patient differences [11]. Also in this study, the incidence of influenza varied from 0% to 57% of all RTI consultations between GPs, and coryza, between 0% and 50%. The same illness labelled as influenza by one GP will be labelled as coryza by another. Studies in which GPs were asked to make a diagnosis in hypothetical cases of LRTI showed that for the same case, some GPs would diagnose acute bronchitis, others pneumonia and others URTI [12, 13].

It is in the patient in the community, who is usually not severely ill and has an illness both characterised and dominated by cough, in which the greatest uncertainty exists. This syndrome is either labelled as AB, acute cough syndrome or, more recently, lower respiratory tract illness [14]. The term “acute bronchitis” is in popular use, but has been used to describe a variety of acute clinical syndromes, usually in patients without known chronic lung disease. These may include one or more of up to 20 clinical symptoms [15, 16] and either include [17] or exclude [6] the expectoration of purulent sputum and chest clinical signs [18, 19]. Cough is the one common feature to all studies of AB. However, there is no consensus about its duration; it ranges from an average of only 13 days [20] to a minimum of more than 2 weeks [17, 21]. The speed of cough resolution varies from trial to trial, confirming the heterogeneity of these cough syndromes [22]. As many as one third of patients initially labelled as AB [17, 23–25] and two thirds with recurrent AB [26], are subsequently found to be suffering from asthma.

One group [27] has developed a definition designed to capture those given antibiotics for LRTI while excluding URTI. This includes all of the following. 1) New or increasing cough, productive of sputum and associated with another symptom or sign of LRTI, including shortness of breath, wheeze, chest pain or new focal or diffuse signs on chest examination. 2) One or more constitutional symptom, including fever, sweating, headaches, aches and pains, sore throat or coryza. 3) Antibiotics prescribed for the illness. This definition has subsequently been simplified [14] to all of the following: 1) an acute illness present for  $\leq 21$  days or less; 2) cough as the cardinal symptom; 3) at least one other lower respiratory tract symptom (sputum production, dyspnoea, wheeze, chest discomfort/pain); 4) no alternative explanation *e.g.* sinusitis,

asthma. This approach has the advantage of using a symptom-based complex that is definable and reproducible within everyday practice situations and beyond, to research studies. It has the potential to overcome the problems of anatomically based definitions, but has the disadvantage of being new and therefore not widely used.

One cause of cough and AB is influenza virus infection. Influenza is generally believed to have a unique symptom constellation, which allows its separation from AB [28]. Recent studies have cast doubt on the accuracy of clinical influenza diagnosis. In the neuraminidase inhibitor trials, it was necessary to develop a clinical definition that allowed accurate patient identification. Such definitions were based on the presence of fever (variably defined) together with the presence of one or two or more of headache, myalgia, cough, sore throat [29–33], sometimes with sweats/chills, fatigue, nasal symptoms and malaise [34, 35]. Laboratory confirmation of influenza in these studies ranged from only 57% [32] to 78% [30] of cases, suggesting that between one quarter and one half of such clinical cases did not have influenza virus infection. These studies were always performed when influenza virus was known to be circulating in the community (information that is not always available to the physician) and included predominantly young people. In a separate, smaller study performed in Dutch general practices during one winter, using a similar clinical definition, only 52% of patients were influenza virus positive [36]. In this study, the use of cough, headache, feverishness and vaccination status had a positive predictive value of 75% for confirmed influenza virus infection. This was better than that for the International Classification of Health Problems in Primary Care and the Netherlands Institute of Primary Health Care definitions (54% and 52%, respectively), but only as good as GP judgement (76%). Again, older patients were few in number. Similar results have been found when analysing symptoms in the neuraminidase studies [37], in which severity grading of symptoms has improved prediction accuracy [38].

Overlap with the symptoms of other viral infections is one explanation for the inaccuracy of clinical influenza prediction. Respiratory syncytial virus infection accounted for 10–24% of cases of influenza-like illness in a study of patients performed over three winters in British general practices. The frequency of laboratory-confirmed influenza was 24–45% [39].

Diagnosis in the elderly may be even more difficult. In a study of patients aged  $\geq 65$ , who were admitted to hospital with LRTI, a combination of cough, a temperature of  $\geq 38^{\circ}\text{C}$  and an illness duration of  $< 7$  days were the best features for determining those with influenza. However, although the negative predictive value was 91%, the positive predictive value was only 47% and no feature or combination of features could be used to clearly separate cases [40].

In CAP the lung parenchyma is invaded by inflammatory cells and secretions which form consolidation. These histopathological changes are usually visualised as shadowing on a chest radiograph, and this is used as the “Gold standard” for pneumonia diagnosis in most studies. This, however, is a limitation for patients seen in the community, where chest radiographs may not be readily available and a diagnosis based on clinical features is required.

Studies have evaluated the use of clinical symptoms and signs against the standard of chest radiograph shadowing. All are limited by inter-observer variation in the ability

to elicit signs [8]. Patients labelled with other LRTI syndromes are found to have CAP and those labelled as CAP may have a normal radiograph [41–45]. No symptoms, signs or combinations of these are accurately predictive of radiograph shadowing. A number of clinical features of pneumonia are statistically significantly associated with the presence of such shadowing, but even “textbook features” of pneumonia, such as dullness to percussion, bronchial breathing and aegophany, exhibit a high specificity but have a sensitivity that is too low to be clinically useful [7, 43, 44, 46–48]. These features were present in only 5%, 8% and 9% of cases in three studies of adults with CAP in the community [49–51]. Predictive rules made up of combinations of these features can be used in research studies, but even then they may operate differently in different settings because of varying pneumonia prevalence. Predictive rules derived from an emergency room-attending population may not be applicable to a primary healthcare setting based in the community [52–57]. They are not useful for the individual patient because of impracticality and a sensitivity which is inferior to physician judgement [58]. It is not surprising, then, that physicians’ thresholds for ordering chest radiographs in patients who might have CAP vary [59, 60], meaning it’s a limitation in community studies in which the definition of CAP relies on chest radiographic shadowing.

One approach has been to use the presence of focal chest signs in a patient with other features of LRTI, as a predictor of radiographic shadowing. In one study, 39% of such patients were confirmed to have radiographic shadowing, compared to 2% in those without such focal signs [42]. However, the total number of CAP cases in those without focal signs (because many more do not have such signs) was the same as in those with focal signs. While insensitive, this approach has the advantage of simplicity.

The clinical relevance of radiographic shadowing is unclear. In a community study of 581 adults with RTI, of the 20 cases with radiographic CAP, only seven were clinically diagnosed and a further 15 with clinical “pneumonia” showed no radiographic shadowing [45]. Moreover, patients without radiographic CAP shared other features with the radiographic CAP group, such as raised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white cell count and serological evidence of pneumococcal or mycoplasma infection. There is inter-observer variability in chest radiograph interpretation [61, 62] and radiographic consolidation could be present on CT scanning when the chest radiograph appears to be normal [63], and might therefore just be a marker of illness severity in this group.

AECOPD and AEBX occur with a background of chronic disease state. These chronic conditions have their own definitions, which are beyond the scope of this document. There is no accepted definition of what constitutes an exacerbation of either condition. AECOPD is not defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [64]. The British Thoracic Society (BTS) guidelines refer to “a worsening of the previously stable situation” with symptoms that may include increases in sputum purulence, sputum volume, dyspnoea and wheeze, and chest tightness and fluid retention [65]. A recent consensus statement described “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medications” [66]. Perhaps the most widely used definition of AECOPD is symptom based, and depends on the presence of one or more of the following:

increased sputum purulence, increased sputum volume and or increased dyspnoea (with, if only one of these three is present, one or more additional symptom from sore throat, nasal discharge, fever, increased wheeze or cough or increased respiratory or heart rate by 20% above baseline) [67]. A more recent approach has been to define AECOPD as any two major symptoms (dyspnoea, sputum purulence, sputum amount) or one major and one minor (nasal discharge/congestion, wheeze, sore throat, cough) on two consecutive days [68]. Others have simply used “in the clinician’s opinion” [69]. AEBX has been defined as subjective and persistent deterioration in at least three respiratory symptoms (including cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain) with or without fever, radiographic deterioration, systemic disturbances or deterioration in chest signs [70].

Before the time of presentation with an acute exacerbation (AE), the definitive diagnosis of underlying disease may not have been made. This could be because this is the first presentation for that disease and it may be complicated by lack of precision in the application of diagnostic labels, *e.g.* the use of asthma for COPD. While some assessment of the likely underlying disease has to be made at presentation, this may be inaccurate. Both the diagnosis of COPD and bronchiectasis may be suggested by the clinical history but confirmation by objective testing is required. This may be both impossible/impractical (*e.g.* spirometry for COPD, high-resolution computed tomography (HRCT) for bronchiectasis) and inaccurate in the acute setting. The chest radiograph has a sensitivity ranging from 0–37% [71, 72] in the detection of the irreversible abnormal dilatation of one or more the bronchi, which defines bronchiectasis. A recent study of HRCT in AECOPD found a frequency of undiagnosed bronchiectasis of 29% [73], suggesting significant diagnostic overlap.

In summary, the LRTI syndromes can be separated with a varying degree of precision, depending on the setting and access to investigations. In the community, it might, in the future, be appropriate to move towards the use of the generic lower respiratory tract illness, rather than separate the syndromes. However, since these labels are in widespread use, despite the absence of both clear clinical separation and agreed definitions of these syndromes, these terms will continue to be used and are therefore used in these guidelines.

Table 27 Introduction, methods and definitions: evidence table

1st author/study group [ref.]	Objective	Design	Evidence level
HUESTON [6]	To define clinical features separating AB from viral URTI	RCS	4B+
METLAY [7]	To assess predictive value of clinical criteria for diagnosis of pneumonia	SR	1B+
WIPF [8]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3A+
HOPE-SIMPSON [9]	To determine GP definitions of acute respiratory infections	PCS	3B+
COENEN [10]	To investigate decisions about antibiotic prescription for cough in general practice	Consensus	6A-

1st author/study group [ref.]	Objective	Design	Evidence level
HOWIE [11]	To describe factors influencing antibiotic use for respiratory illness in general practice	RCS	4C-
VERHEIJ [12]	To determine GP definitions of acute respiratory infections	PCS	3C+
STOCKS [13]	To determine GP definitions of acute respiratory infections	PCS	3A?
MACFARLANE [14]	To determine incidence aetiology and outcome of LRTI	PCS	3B+
BOLDY [15]	To describe features of AB	PCS	3A+
GONZALES [16]	To describe clinical features of AB and those features associated with antibiotic Rx	PCS	3B-
THIADENS [17]	To investigate association between asthma and AB	PCS	3B+
OEFFINGER [18]	To determine how GP's diagnose AB	PCS	3C+
BENT [19]	To perform meta-analysis of antibiotic placebo RCTs in AB	SR	1B+
VERHEIJ [20]	To describe clinical course of AB	PCS	3A-
THIADENS [21]	To assess predictive value of PEFV in diagnosis of airflow obstruction in those presenting with acute cough	PCS	3A-
FAHEY [22]	To assess effectiveness and side-effects of antibiotics in acute cough	SR	1B-
WILLIAMSON [23]	To determine frequency of atopic disease in AB	RCS	4B+
MELBYE [24]	To determine frequency of airflow obstruction and reversibility in acute RTI	PCS	3C+
JONSSON [25]	To identify frequency of asthma/COPD in patients with AB	RCS	4C+
HALLETT [26]	To assess frequency of asthma in patients with AB	PCS	3B+
MACFARLANE [27]	To determine microbial aetiology and outcome of LRTI in the community	PCS	3A+
FLEMING [28]	To assess the predictive value of clinical signs and symptoms in influenza	PCS	3B+
HAYDEN [29]	To evaluate efficacy and safety of zanamivir in influenza	RCT	2A+
MAKELA [30]	To evaluate efficacy and safety of zanamivir in influenza	RCT	2A+
MATSUMOTO [31]	To evaluate efficacy and safety of zanamivir in influenza	RCT	2A+

1st author/study group [ref.]	Objective	Design	Evidence level
MONTO [32]	To evaluate efficacy and safety of zanamivir in influenza	RCT	2A+
The Management of Influenza in the Southern Hemisphere Trialists Study Group [33]	To evaluate efficacy and safety of zanamivir in influenza	RCT	2A+
NICHOLSON [34]	To evaluate efficacy and safety of oseltamivir in influenza	RCT	2A+
TREANOR [35]	To evaluate efficacy and safety of oseltamivir in influenza	RCT	2A+
VAN ELDEN [36]	To assess predictive value of clinical signs and symptoms in influenza	PCS	3A+
MONTO [37]	To assess predictive value of clinical signs and symptoms in influenza	RCS	4A+
ZAMBON [38]	To assess predictive value of clinical signs and symptoms in influenza	PCS	3A+
ZAMBON [39]	To assess role of RSV in influenza-like infection	PCS	3B+
WALSH [40]	To assess predictive value of clinical criteria for diagnosis of influenza	PCS	3B+
HECKERLING [41]	To assess predictive value of clinical criteria for diagnosis of pneumonia	RCS	4B+
WOODHEAD [42]	To determine aetiology and outcome of CAP in the community	PCS	3A+
MELBYE [43]	To assess predictive value of clinical and laboratory criteria for diagnosis of pneumonia	PCS	3A+
MELBYE [44]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3A+
MELBYE [45]	To compare CXR positive with CXR negative LRTI	PCS	3B+
CHRISTENSEN-SZALANSKI [46]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3A+
MELBYE [47]	To assess diagnostic value of history, examination and blood tests in the diagnosis of pneumonia	PCS	3B+
GENNIS [48]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3B+
SHAW [49]	To describe causes of severe chest	PCS	3B+

1st author/study group [ref.]	Objective	Design	Evidence level
EVERETT [50]	infection at home To describe causes of major chest infection at home	PCS	3B+
WOODHEAD [51]	To describe multiple studies of CAP	Other	Various
DIEHR [52]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3A+
HECKERLING [53]	To validate clinical prediction rule for pneumonia	RCS	4B+
HECKERLING [54]	To compare predictors of pneumonia in three geographical settings	PCS	3B+
MEHR [55]	To identify clinical findings associated with pneumonia in nursing home residents	PCS	3B+
TAPE [56]	To analyse regional variations in pneumonia diagnosis	PCS	3B+
MELBYE [57]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3B+
EMERMAN [58]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3B+
HECKERLING [59]	To investigate physician's predicted probabilities of pneumonia and its relation to CXR ordering rate	PCS	3B+
CHRISTENSEN- SZALANSKI [60]	To assess predictive value of clinical criteria for diagnosis of pneumonia	PCS	3A+
YOUNG [61]	To assess impact of experience on inter-observer variability in CXR reading	PCS	3A+
MELBYE [62]	To assess inter-observer variability in chest radiograph diagnosis of pneumonia	PCS	3A+
SYRJALA [63]	To compare HRCT and CXR in diagnosis of pneumonia	PCS	3A+
PAUWELS [64]	NHLBI/WHO COPD Guidelines	Exp.	6C
The COPD Guidelines Group of the Standards of Care Committee of the BTS [65]	BTS COPD Guidelines	Exp.	6C
RODRIGUEZ-ROISIN [66]	Consensus statement	Exp.	6C
ANTHONISEN [67]	To study antibiotic <i>versus</i> placebo	RCT	2A+

1st author/study group [ref.]	Objective	Design	Evidence level
SEEMUNGAL [68]	in exacerbations of COPD To assess effect of exacerbations of COPD on health-related quality of life	PCS	3A+
BALL [69]	To seek factors affecting Rx failure	RCS	4B+
TSANG [70]	To compare two antibiotics in treatment of bronchiectasis	RCT	2A-
SILVERMAN [71]	To compare CT with bronchograms in diagnosis of bronchiectasis	PCS	3A+
COOKE [72]	To assess sensitivity and specificity of CT in diagnosis of bronchiectasis	PCS	3A+
O'BRIEN [73]	To study heterogeneity of COPD diagnosed in primary care	PCS	3A+

As references [1–5] relate to methodology and are not used as evidence for recommendations, they have not been included in this table. AB: acute bronchitis; URTI: upper respiratory tract infections; RCS: retrospective cohort study; SR: systematic review; PCS: prospective cohort study; GP: general practitioner; LRTI: lower respiratory tract infection; Rx: treatment; RCT: randomised controlled trial; PEFr: peak expiratory flow rate; RTI: respiratory tract infection; COPD: chronic obstructive pulmonary disease; RSV: respiratory syncytial virus; CAP: community-acquired pneumonia; CXR: chest radiograph; HRCT: high-resolution computerised tomography; NHBLI: National Heart, Lung, Blood Institute; WHO: World Health Organization; Exp.: expert opinion; BTS: British Thoracic Society.

## **APPENDIX 2: DESCRIPTIVE EPIDEMIOLOGY, MICROBIOLOGY AND RISK FACTORS**

### *Descriptive epidemiology*

It is usual to state that LRTIs occur at all ages and are responsible for considerable morbidity and mortality. However, there are only a limited number of reports on morbidity and mortality by respiratory infectious diseases, due in part to their varying frequency and the fact that most never reach hospital, being managed by the general practitioner (GP) or never reaching medical attention. Of all RTIs about one third are thought to involve the lower respiratory tract, the remaining two thirds affecting the upper respiratory tract.

### Incidence

The only studies to document the frequency of LRTIs in the adult population suggest an annual incidence of 51/1000 to 84/1000 for LRTI [14, 27, 42] and 1.6/1000 to 19/1000 for pneumonia [42, 74–80]. Flu or flu-like syndromes occur each year in 0.4–2.1% of the population and may account for 0.5–2/1000 hospitalisations and up to 1.5/1000 deaths [81–83].

Variations in the frequency of LRTI and CAP between studies can be explained by differences in the methods used to assess incidence as well as in the geographical situation and age range of studied populations.

Nevertheless, extrapolation from these figures suggests that each year in adults in France, Germany, Italy, Spain and the United Kingdom there are between one and three million cases of community-acquired pneumonia (CAP) and between 12 and 20 million cases of LRTI. Increasing age is associated with a greater incidence of LRTI [1, 76, 84].

The morbidity from LRTIs is especially difficult to evaluate. In the United Kingdom respiratory infections are the commonest reason for GP consultation [85], accounting for 6% of all consultations and 4.4% of all hospital admissions [86]. Hospital admission varies according to clinical diagnosis and country occurring in between 22% and 51% of patients with CAP [42, 74, 87] to as few as 1–5% of those with LRTI [27, 88]. One study by LOVERING *et al.* found that the annual incidence of hospitalisations for LRTI varied between 15/10 000 in the 16–40 years age range to more than 300/10 000 in subjects older than 79 years [84]. Mean incidence of hospitalisations was 62.3/10 000 in that study. Pneumonia accounted for 37% of all hospitalisations for LRTI, and 41% of patients had a pre-existing respiratory disease.

### Mortality

In developing countries respiratory infections remain the first cause of mortality, particularly in infants. In developed countries, while mortality has declined spectacularly during the twentieth century, LRTIs remain a leading cause of death. WHO statistics estimate that mortality from respiratory infections is 48/100 000 worldwide and ranges from 40 to 50/100 000 in Europe (WHO's 2002 annual report at <http://www.who.org/>). These figures contrast with a much higher mortality from LRTI in developing countries (up to 100–150/100 000 in some countries from south-east Asia or Africa).

A more precise idea of the mortality rate from pneumonia comes from European prospective studies which show an average mortality of 5–15% for those hospitalised rising to 15–25% for pneumococcal pneumonia with bacteraemia, 20–45% for pneumonia requiring admission to the ICU and about 40% in patients older than 80 years [75, 80, 89–99]. The number of deaths due to influenza virus varies from 25 to 480/100 000 [100].

Such figures stress the importance of early recognition of those patients who are severely ill or at risk of becoming severely ill. A number of studies have sought risk factors for pneumonia severity and a few have also sought risk factors for pneumonia occurrence. While some factors may be significant for both, it is important not to confuse these issues. For example, age is an independent risk factor for pneumonia occurrence in some studies [101] and is also a risk factor for pneumonia severity in others; however, this association may disappear in multivariate analyses [102]. This and other risk factors for occurrence will be discussed in more detail in the following sections.

### **Microbiology**

Involved pathogens

Wide variations between studies in the frequency of each micro-organism 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.

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; on the other hand multiple organisms may be found in up to 10% of cases or more. Age >70 years, renal and cardiac co-morbid illnesses and non alveolar infiltrates are independently associated with a higher proportion of unknown aetiology in 204 patients hospitalised for CAP [103].

Table 28 summarizes the microbiological aetiologies of LRTI in the community. Studies have investigated the microbiological causes of outpatients with CAP (table 29) and of patients admitted to hospital (table 30) or to the intensive care unit (table 31). Most studies in mild infections suggest that microbial aetiologies in outpatients are similar to that of hospitalised patients [1, 79, 91, 93, 94, 104–126].

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* (*Staph. aureus*), *Moraxella catarrhalis*. Among intracellular bacilli *Mycoplasma pneumoniae* (*M. pneumoniae*) is the most common, followed in frequency by *Legionella* and *Chlamydia* species, with viruses being involved in 5 to 20%. In ICU, *Staph. aureus*, Gram-negative bacilli and *Legionella sp* are more frequently encountered.

TABLE 28 Aetiology of lower respiratory tract infection in the community (%)

1 <sup>st</sup> author/study group [ref.]	Subjects n	<i>S pneumoniae</i>	<i>H influenzae</i>	<i>M catarrhalis</i>	<i>Staph aureus</i>	Gram negative bacilli	<i>M pneumoniae</i>	All <i>chlamidiae</i>	<i>C pneumoniae</i>	<i>C burnetii</i>	All Virus	<i>Influenza</i>
BOLDY [15]	42	3.0	3.0	3.0	0	0	8.0	0		0	21.0	10.0
EVERETT [50]	187						6.0	2.0		0	6.0	4.0
FRANSEN [211]	78	8.0	3.0		3.0	0	3.0				20.0	12.0
MACFARLANE [27]	206	30.0	8.0	2	1.0		0.5			0.5	8.0	5.0
MACFARLANE [14]	316	17.1	9.8	2.2			7.3		17.4		19.3	7.3
MARDH [212]	101						16.0				2.0	0
SHAW [49]	40	16.0	14.0		10.0	0	5.0	3.0		0	11.0	11.0
Range		3-30	3-14	2-3	1-10	0	0.5-16	0-3		0-0.5	2-21	0-12

TABLE 29 Aetiology of community-acquired pneumonia in the community (%)

1 <sup>st</sup> author/study group [ref.]	Subjects n	<i>S pneumoniae</i>	<i>H influenzae</i>	<i>L pneumophila</i>	<i>M catarrhalis</i>	<i>Staph aureus</i>	GNEB	<i>M pneumoniae</i>	All clamydiae	<i>C pneumoniae</i>	<i>C psittaci</i>	<i>C burnetii</i>	All Virus	Influenza
ALMIRALL [87]	105	12.4	0	2.9		0	0	7.6	15.2	15.2	0	0	11.4	0
ALMIRALL [75]	232	11.6	0.4	2.2		0	0.4	3.9	0	9.5	0	2.2	14.2	8.2
BERNTSSON [213]	54	9.3	11.1	0		–	–	37.0	3.7	–	3.7	0	13.0	7.4
BLANQUER [214]	48	12.5	0	12.5		0	0	12.5	–	–	0	0	20.8	14.6
British Thoracic Society [191]	67	6.0	0	0	0	0	0	3.0					28.0	10.0
DULAKE [215]	36	19.0	14.0			0	0	2.0	0			0	2	2
FOY [216]	2256	12.0						20.0					25.0	8.0
JOKINEN [79]	345	36.2	3.5		2.3			8.7	10.7	8.7				
MARRIE [118]	149							22.8		10.7		2.7		2.7
MELBYE [45]	36	11.1	0	0		–	–	13.9	8.3	8.3	0	–	33.3	19.4
MICHETTI [121]	119	0	0	3.4		0	0	32.8	16.0	6.7	9.2	0	5.9	3.4
WOODHEAD [42]	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	0–2	0–1	0–1	1–33	0–16	7–15	0–9	0–3	2–33	0–19

TABLE 30 Aetiology of community-acquired pneumonia in adults admitted to hospital (%)

1 <sup>st</sup> author/study group [ref.]	Subjects n	<i>S pneumoniae</i>	<i>H influenzae</i>	<i>L pneumophila</i>	<i>Staph aureus</i>	<i>Mcat</i>	GNEB	<i>P aeruginosa</i>	<i>M pneumoniae</i>	All clamidiae	<i>C pneumoniae</i>	<i>C psittaci</i>	<i>C burnetii</i>	All Virus	Influenza
ARANCIBIA [198]	559	13.8	5.0	5.2			10.7	7.0	1.8	9.5	7.7	0.2	1.6	2.8	
AUBERTIN [217]	274	12.4	3.3	10.6	2.2	0.0	2.9		8.8	–	–	2.6	0.7	2.6	0.0
AUSINA [218]	207	39.1	1.0	6.3	0.5	0.0	2.9		16.9	–	–	6.3	2.4	3.9	2.4
BERNTSSON [219]	127	54.3	3.9	0.8	0.8	0.0	0.0		14.2	–	–	2.4	0.0	18.1	12.6
BLANQUER [214]	462	14.7	1.9	13.9	1.7	0.0	3.2		3.5	–	–	0.2	0.6	13.0	7.8
BLASI [106]	207	7.7	2.4	4.8	3.9	1.0	5.3		8.2	10.1	10.1	0.0	0.0	–	–
BOHTE [107]	334	26.9	7.8	2.4	1.2	1.5	3.3		5.7	–	–	–	0.3	8.1	4.2
British Thoracic Society [191]	453	34.0	5.7	2.0	0.9	0.0	0.9		17.9	–	–	2.9	1.1	7.1	7.1
BURMAN [ 220]	196	32.1	4.6	2.0	1.5	1.5	1.0		8.7	–	–	3.1	0.0	21.9	8.7
FALCO [185]	400	21.0	3.3	7.5	0.0	0.0	2.0		2.3	–	–	2.8	0.0	–	–
GINESU [110]	520	10.8					32.9		0.4					0.9	
GOMEZ [111]	342	12.6	5.6	1.5	0.0	0.3	0.0		3.2	6.1	6.1	0.0	0.0	–	–
HOLMBERG [221]	147	46.9	9.5	2.7	0.7	2.0	0.0		5.4	–	–	1.4	0.0	10.9	10.2
HONE [222]	50	20.0	16.0	4.0	0.0	2.0	2.0		4.0	–	–	0.0	0.0	20.0	10.0
LEVY [169]	116	25.9	11.2	4.3	2.6	0.9	6.9		3.4	–	–	0.9	0.0	4.3	–
LOGROSCINO [115]	613	5.9	3.6	2.8	1.1	0.8	3.9		3.3	0.0	4.2	–	–	3.1	–
LORENTE [116]	114	35.1	0.9	1.8	2.6	0.0	2.6		9.6	0.0	1.8	–	0.9	–	–
MACFARLANE [223]	127	75.6	3.1	15.0	2.4	0.0	0.8		2.4	–	–	5.5	0.8	8.7	5.5
MCNABB [224]	80	50.0	6.3	1.3	3.8	0.0	1.3		0.0	–	–	0.0	0.0	6.3	6.3
MENENDEZ [120]	184	23.9	1.6	0.5	0.0	0.0	1.6		14.1	0.0	0.5	0.0	1.1	1.6	1.6
MICHETTI [121]	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
ORTQVIST [170]	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 [225]	254	13.8	6.3	3.1	0.4	0.8	2.0		3.9	–	–	1.2	0.0	–	–
PAREJA [226]	165	7.3	1.8	2.4	2.4	0.0	27.3		10.3	–	–	1.2	10.9	18.2	13.3
RUF [227]	442	15.4	2.5	3.8	2.7	0.0	2.5		9.3	–	–	3.2	0.0	8.8	4.1
RUIZ [123]	395	16.5	6.3	4.3	1.8	1.0	6.3		3.3	0.0	3.8	0.5	2.8	9.9	5.8
SOCAN [124]	211	5.7	0.9	2.8	0.5	0.0	1.9		5.7	0.0	18.0	0.9	0.5	24.2	–
SOPENA [125]	330	20.3	2.1	13.9	0.6	0.0	0.3		1.5	0.0	15.8	0.0	1.2	–	–
STEINHOFF [126]	237	8.6					5.1		6.3		7.7			6.3	
WHITE [228]	210	11.4	1.9	1.4	3.8	0.0	1.4		14.3	–	–	1.4	2.9	14.8	12.4
Range (median)		6–76	1–16	1–14 (3.1)	0–4 (0.5)	0–2	0–33 (2.0)		0–18	0–10	0–18	0–6	0–10.9	1–24	0–13

TABLE 31 Aetiology of community-acquired pneumonia in adults admitted to ICU (%)

1 <sup>st</sup> author/study group [ref.]	Subjects n	<i>S pneumoniae</i>	<i>H influenzae</i>	<i>L pneumophila</i>	<i>Staph aureus</i>	GNEB	<i>M pneumoniae</i>	All clamidiae	<i>C psittaci</i>	<i>C burnetii</i>	All Virus	<i>Influenza</i>
ALKHAYER [229]	18	16.7	0	11.1	5.6	0	0	5.6	5.6	0	16.7	0
ALMIRALL [89]	58	17.2	1.7	8.6	0	6.9	0	1.7	1.7	0	1.75	–
British Thoracic Society [173]	60	18.3	11.7	11.7	5	3.3	6.7	0	0	0	8.3	5.0
EL SOLH [109]	57	14	7	9	7	14						2
GOWARDMAN [91]	32	18.4			9.2	11.6						
HIRANI [113]	57	17.5	0	15.8	12.3	1.8	0	5.3	5.3	0	10.5	8.8
LEROY [230]	299	26.8	8.7	0	19.1	15.1	0.7	1.7		0	–	–
MOINE [175]	132	32.6	10.6	3.0	3.8	10.6	0.8	0.8	0.8	1.5	5.35	1.5
OLAECHEA [122]	262	11.5	3.8	8.0	3.8	3.1	3.1	1.5	1.5	0	1.95	–
ORTQVIST [231]	53	17.0	1.0	9.0	0	7.0	0	2.0		0	0	
PACHON [172]	67	17.9	3.0	10.4	1.5	6.0	0	0	0	0	1.5	1.5
RELLO [232]	58	22.4	0	13.8	0	8.6	0	0	0	0	1.75	1.7
SORENSEN [233]	36	33.3	8.33	8.3	8.3	2.8	0	0	0	0	13.9	2.8
TORRES [180]	92	15.2	0	14.1	1.1	9.8	6.5	0	0	0	–	–
WOODHEAD [171]	50	32	0	30.0	10	0	2	0	0	0	8.0	4.0
Range (median)		12–33	0–12	0–30 (9.0)	0–19 (3.8)	0–15 (6.0)	0–7	0–6	0–6	0–2	0–17	0–9

Table 32 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 influence of the baseline level of lung function on pathogens found in sputum samples [127, 128] (figure 3). 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) [129]. Respiratory viruses are more frequently found in induced sputum of hospitalised patients with COPD exacerbations than in control stable COPD subjects (47% vs 10%), the most frequent viruses being rhinovirus, influenza A 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 [130]. Finally, bacterial exacerbations of COPD could be related to the appearance of new strains of *S pneumoniae*, *H influenzae* or *M catarrhalis* in the colonised airways [131].

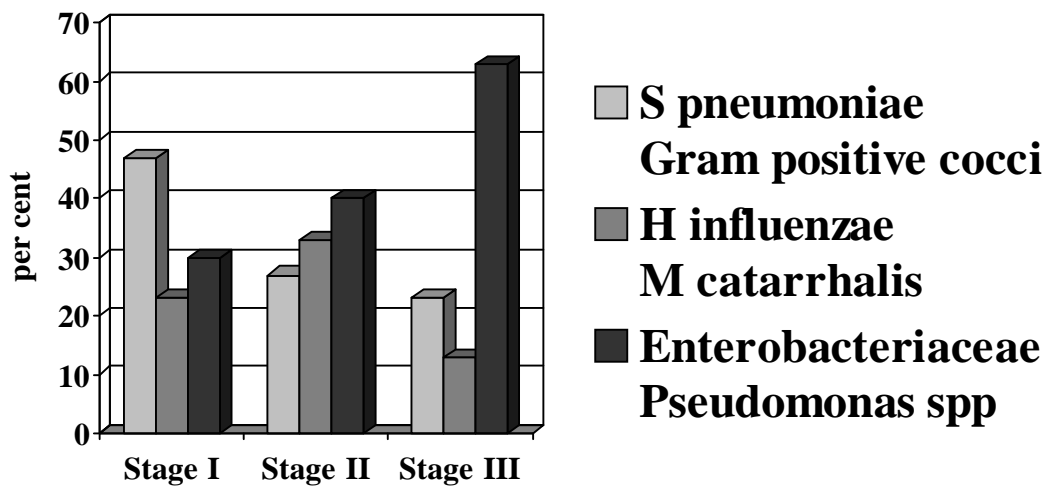


FIGURE 3. Effect of the level of lung function on the distribution of 3 groups of bacteria involved in exacerbations of COPD, as assessed by sputum microbiological examination. (stage I, FEV<sub>1</sub> ≥ 50% of predicted value; stage II, FEV<sub>1</sub> > 35% to < 50% of predicted value; stage III, FEV<sub>1</sub> ≥ 35% of predicted value). Reproduced from [127] with permission from publisher.

TABLE 32 Aetiology of exacerbations in patients with COPD (%)

1 <sup>st</sup> author/study group [ref.]	Sample	Subjects n	<i>S pneumoniae</i>	<i>H influenzae</i>	<i>M catarrhalis</i>	<i>Staph aureus</i>	GNEB	<i>P aeruginosa</i>	<i>M pneumoniae</i>	All <i>chlamidiae</i>	<i>C pneumoniae</i>	<i>C psittaci</i>	<i>C burnetii</i>	All Virus	Influenza	Para- influenza	Rhino-virus	Respiratory syncytial virus
BEATY [234]	Serology	44									4.5							
CARILLI [235]	Serology	46							8.7						8.7	4.3	0	17.4
EADIE [236]	Serology	47													4.3	2.1	23.4	0
ELLER [127]	Sputum	211	9	7.6	–	7.1	18.9	6.6										
FAGON [237]	PSB	54	8	26	3.5	4.5	6	3.5										
GUMP [238]	Serology	116	27.6	42.24	10.3	21.6	6.9	0.8						33.6	12.9	7.8	3.4	4.3
KARNAK [239]	Serology	38									34.0							
LAMY [240]	Serology	49							2.0						28.6	24.5		6.1
LIEBERMAN [241]	Serology	62									11.3							
MCNAMARA [242]	Serology	42							9.5						0	0	42.8	11.9
MIRAVITLES [128]	Sputum	91	10	22	9		7	15										
MOGULKOC [243]	Serology sputum	49	8.2	8.2	6.1				6.1		22.4							
MONSO [244]	PSB	29	10.3	34.5	6.9			6.9										
ROSS [245]	Serology	125		0					0			0	0		10.4	1.6	3.2	
SEEMUNGAL [246]	Serology Culture	168							0		0.6				5.4	0.6	23.2	
SOLER [247]	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	3–10	4–22	6–19	0–18	0–10		0.34				0–29	0–25	0–43	0–17

Only a few studies assessed the microbiological pattern of airway colonization in bronchiectasis, and no study has investigated microbiological aetiology of exacerbations. Main results are provided in table 33 in steady state bronchiectasis; they highlight the high frequency of *Pseudomonas* infection, particularly in case of impaired lung function.

TABLE 33 Microorganisms isolated in patients with non-cystic fibrosis bronchiectasis (%)

1 <sup>st</sup> author/study group [ref.]	Subjects n	Sample	<i>S pneumoniae</i>	<i>H influenzae</i>	<i>M pneumoniae</i>	<i>P aeruginosa</i>	Other GNEB	<i>Staph aureus</i>	Mycobacteria
ANGRILL [132]	75	PSB	8	32	4	15	3	3	–
CHAN [248]	32	Sputum	–	19	–	34	19	–	–
HO [133]	100	Sputum	6	10	2	33	5	5	3
O'DONNELL [249]	349	Sputum	–	–	–	25	–	–	–
Range			6–8	10–19	2–4	15–34	5–19	3–5	

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 colonisation with pathogenic bacteria, mainly *H. influenzae* and *P. aeruginosa* (Odds ratio: 3.92, 3.91 and 4.80, respectively) [132]. In a study of 100 patients with steady-state bronchiectasis, the presence of *P. aeruginosa* in the sputum was associated with lower FEV<sub>1</sub>/FVC ratio (60% vs 72% in the absence of pathogenic microorganism) and higher volume of daily sputum production (1–6 score : 3 vs 1) [133]. 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).

#### Antibiotic resistance

Antibiotic resistance in micro-organisms is an increasing concern [1, 105, 134–140], particularly the resistance of *S. pneumoniae* (figure 4.), which is by far the most commonly documented cause of respiratory infection and which is associated with a high morbidity and mortality.

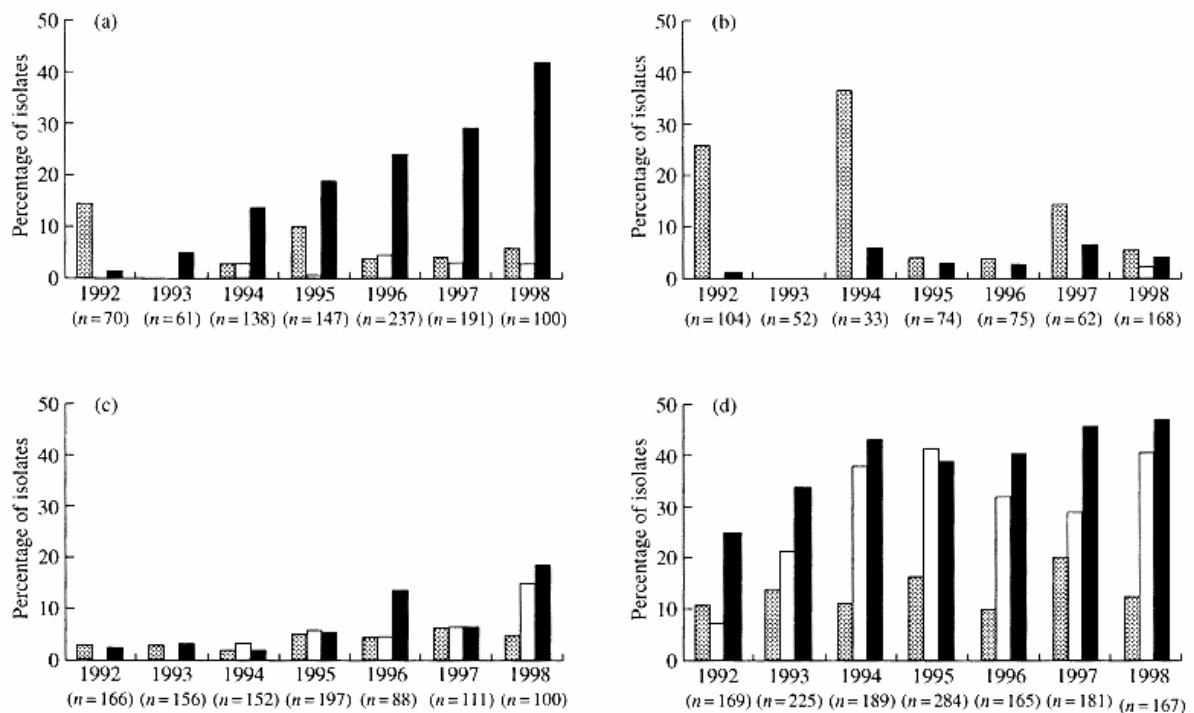


FIGURE 4. Growing resistance of *Streptococcus pneumoniae* in isolates from Europe. Reproduced from [140] with permission from publisher. (a): Italy; (b): Germany; (c): UK; (d): France. ▨: Penicillin intermediate; □: penicillin resistant; ■: erythromycin resistant.

However, there are important differences between countries or regions within a country. Tables 34 and 35 and figure 4 present 1998 data from the Alexander network (a collaborative worldwide project on antibiotic resistance) on the resistance of *S. pneumoniae* and *H. influenzae* in Europe [140]. Table 36 presents 2002 data from the The European Antimicrobial Resistance Surveillance System (EARSS) on the resistance of *S. pneumoniae* to penicillin and macrolides [<http://www.earss.rivm.nl/>]

and Table 37 on tetracycline resistance in *S. pneumoniae* from various publications. The EARSS network identified the largest proportions of penicillin non-susceptible *S. pneumoniae* (PNSP) in France, Israel, Poland, Romania and Spain. The smallest proportions of PNSP were reported from the north of Europe, but also from central European countries such as Germany and Austria. Even though the average proportion of PNSP was 11% for all the isolates reported in 2002, the average proportion of isolates fully resistant ( $\text{MIC} \geq 2 \text{ mg}\cdot\text{L}^{-1}$ ) to penicillin was only 2%. But, large variations in the proportion of PNSP, from <1% in Estonia and Malta to 53% in France and variations in the proportion of fully penicillin resistant isolates, which ranged between 0% and 10% (Spain), were found between countries. In parallel, resistance to erythromycin was observed when in 1% to 42% of *S. pneumoniae* isolates when national data of European countries are considered, and up to 65% of isolates in some areas of Italy (which has a national level of resistance of 42%). In the study by EWIG *et al.* [134] in Spain, where 49% of *S. pneumoniae* had a decreased susceptibility to penicillin, resistance to cephalosporin and macrolides occurred in 31% and 27% of isolates, respectively. Tetracycline resistance ranged from 6.6% in the Netherlands to 37.1% in Spain. Lastly, *S. pneumoniae* resistance to new fluoroquinolones was <1%.

TABLE 34 Resistance of *S. pneumoniae* in Europe according to data from the Alexander project, 1998. Reproduced from [140] with permission from publisher.

Country	Number of isolates	Percentage of total isolates			
		Pen-S	Pen-I	Pen-R	Ery-R
The Netherlands	124	96.8	3.2	0.0	2.4
Germany	168	92.9	5.4	1.8	4.2
Belgium	100	92.0	3.04	5.0	34.0
Italy	100	91.0	6.0	3.0	42.0
Switzerland	138	85.5	8.7	5.8	18.8
UK	87	80.5	4.6	14.9	18.4
Poland	144	91.0	5.5	3.5	6.2
Austria	185	87.6	7.6	4.8	11.4
Portugal	129	82.9	7.0	10.1	9.3
Greece	171	68.4	16.4	15.2	18.1
France	167	46.7	12.6	40.7	47.3
Czech Republic	99	92.9	6.1	1.0	1.0
Slovak Republic	72	48.6	20.8	30.6	8.3
Eire	55	67.3	7.3	25.5	12.7

Pen-S, penicillin susceptible ( $\text{MIC} \leq 0.06 \text{ mg}\cdot\text{L}^{-1}$ ); Pen-I, penicillin intermediate ( $\text{MIC} 0.12\text{-}1 \text{ mg}\cdot\text{L}^{-1}$ ); Pen-R, penicillin resistant ( $\text{MIC} \geq 2 \text{ mg}\cdot\text{L}^{-1}$ ); Ery-R, erythromycin resistant ( $\text{MIC} \geq 0.5 \text{ mg}\cdot\text{L}^{-1}$ ).

TABLE 35 Resistance of *H. influenzae* in Europe according to data from the Alexander project, 1998. With permission from [140] with permission from publisher.

Country	Number of isolates	Percentage of total isolates					
		$\beta$ -lactamase positive	BLNAR	Chloramphenicol-resistant	Doxycycline-resistant	Co-trimoxazole-resistant	Cipro/ofloxacin-resistant
France	158	22.2	0	3.2	3.2	14.0	1.9
UK	100	18.0	1.0	4.0	0	7.0	0
Eire	111	17.1	0	1.8	0.9	13.5	0
Greece	50	16.0	0	0	0	20.0	0
Belgium	96	15.6	0	3.1	1.0	5.2	0
Portugal	213	11.7	0	1.4	2.8	13.6	0
Czech Republic	98	14.3	0	1.0	0	15.3	0
Switzerland	105	10.5	0	0	0	21.9	0
Germany	193	6.7	0	0.5	0.5	27.5	0
The Netherlands	141	6.4	0.7	1.4	0	11.4	0.7
Poland	273	4.4	0	0.4	0.4	28.6	0
Austria	153	3.9	0	0	1.3	13.7	0
Italy	100	2.0	0	0	0	11.0	0
Slovak Republic	99	8.1	0	1.0	1.0	19.2	0
Combined	1890	11.6	0.1	1.2	1.0	18.7	0.2

$\beta$ -lactamase positive, MIC of ampicillin  $\geq 4$  mg·L<sup>-1</sup>; chloramphenicol-resistant, MIC of chloramphenicol  $\geq 4$  mg·L<sup>-1</sup>; doxycycline-resistant, MIC of doxycycline  $\geq 4$  mg·L<sup>-1</sup>; co-trimoxazole-resistant, MIC of co-trimoxazole  $\geq 1/19$  mg·L<sup>-1</sup>; cipro/ofloxacin-resistant, MIC of cipro/ofloxacin  $\geq 1$  mg·L<sup>-1</sup>.

TABLE 36 Total number of isolates (n) and the proportion (%) of penicillin nonsusceptible *streptococcus pneumoniae* (PNSP), erythromycin nonsusceptible *streptococcus pneumoniae* (ENSP) by country in 2002. Reproduced from <http://www.earss.rivm.nl/> with permission from the publisher.

Country	PNSP		ENSP	
	n	%	n	%
Austria	71	1	59	10
Belgium	1210	14	1210	34
Bulgaria	25	8	23	9
Czech Republic	144	8	141	4
Germany	232	1	206	14
Denmark	366	4	360	5
Estonia	21	0	17	0
Spain	658	33	615	26
Finland	427	7	411	13
France	580	53	580	58
Croatia	90	19	84	23
Hungary	61	23	57	21
Ireland	277	12	226	13
Israel	177	38	171	12
Iceland	43	5	43	5
Italy	296	11	250	32
Luxembourg	27	22	23	22
Malta	12	0	12	25
Netherlands	851	1	728	7
Poland	10	30	9	67
Portugal	182	20	NA	NA
Romania	10	50	10	10
Sweden	830	2	683	6
Slovenia	101	19	96	10
Slovakia	16	19	14	29
United Kingdom	610	5	362	13
Total	6747	11	5816	17

NA: not available. \* For *S. pneumoniae* France provided aggregated AST data of the two first quarters of 2002 from their national pneumococci surveillance system.

TABLE 37 Tetracycline Resistance of *S. pneumoniae* in Europe from various publications

Country	Years	Number of isolates	Resistant
Europe [250]	1999–2000	1521	24.1
Spain [251]	1999–2000	300	37.1
France [252]	1997	?	25
Belgium [253]	1998–1999	205	22.9

Greece [254]		125	19.2
Italy [255]	1997–1998	92	18.5
Germany [256]	1998–1999	961	13.9
Portugal [139]	1999	312	13.6
Netherlands [257]	1999	?	6.6

MA: meta-analysis (or systematic review); RCT: randomised controlled trial; PCS: prospective cohort study; RCS: retrospective cohort study; CCS: case control study.

**TABLE 38 Descriptive epidemiology, microbiology and risk factors: evidence table**

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
MACFARLANE [27]	To describe Incidence, microbiological aetiology and outcome of community-acquired LRTIs.	PCS	3A+
MACFARLANE [14]	To describe Incidence, microbiological aetiology and outcome of community-acquired LRTIs.	PCS	3B+
WOODHEAD [42]	To describe microbiological aetiology, outcome and prognostic factors of CAP in the community.	PCS	3A+
JOKINEN [74]	To determine the incidence of CAP.	PCS	3B+
ALMIRALL [75]	To describe the incidence, aetiology and outcome of CAP.	PCS	3A+
MARSTON [76]	To describe the incidence, microbiological aetiology and risk factors in hospitalized CAP	RCS	4B+
KOIVULA [77]	To determine the efficacy of pneumococcal vaccine in the elderly.	RCT	2B+
KOIVULA [78]	To describe the prognosis of CAP in the elderly.	PCS	3A+
JOKINEN [79]	To describe the microbiological aetiology of CAP.	PCS	3B+
MONGE [80]	To describe the epidemiology of hospitalized CAP.	RCS	4B+
FLEMING [81]	To give a description of influenza epidemics.	RCS	4B+
KNOTTNERUS [82]	To determine the Incidence of influenza in the community	MA	6B+
SIMONSEN [83]	To describe the epidemiology of influenza-related hospitalisations.	RCS	4B+
ERS Task Force Report. [1]	To produce Guidelines for management of adult community-acquired LRTI	MA	6B+
LOVERING [84]	To describe resource utilization by hospitalized LRTIs and its	RCS	4B+

	determinants.		
OPCS. [85]	To describe the epidemiology of LRTIs/CAP in general practice.	RCS	4B+
ANDERSON [86]	To describe the epidemiology LRTI	RCS	4B+
ALMIRALL [87]	To document the incidence of CAP due to <i>C. pneumoniae</i> .	PCS	3B+
SCHABERG [88]	To study hospitalisation of LRTIs and its determinants.	CSS	4B+
ALMIRALL [89]	To describe prognostic factors of severe CAP.	PCS	3A+
GARCIA-ORDONEZ [90]	Presentation and outcome of hospitalised CAP in the elderly.	PCS	3B+
GOWARDMAN [91]	Presentation, outcome, microbiological aetiology, prognostic factors of CAP.	RCS	4B+
LAURICHESSE [92]	To describe presentation, microbiological aetiology, treatment, outcome, prognostic factors of hospitalized CAP.	PCS	3B+
LEROY [93]	To describe presentation, risk factors, microbiological aetiology, treatment, outcome, prognostic factors of aspiration pneumonia requiring ICU admission.	RCS	4B+
LEROY [94]	To describe presentation, microbiological aetiology, treatment, outcome, prognostic factors of CAP requiring ICU admission in the elderly.	RCS+PCS	3B+
LEROY [95]	To study the impact of ventilator-associated nosocomial pneumonia on outcome of severe CAP.	RCS+PCS	3B+
MARKOWITZ [96]	To document the mortality and prognostic factors of hospitalized CAP.	RCS	4B+
MUFSON [97]	To describe the mortality, prognostic factors, incidence, serotypes, treatment of pneumococcal CAP.	PCS	3B+
RELLO [98]	Microbiological aetiology, outcome and prognostic factors of severe CAP in the elderly.	PCS	3B+
WATANAKUNAKORN [99]	To describe the presentation, risk factors, outcome, prognostic factors of bacteremic pneumococcal pneumonia.	RCS	4B+
CARRAT [100]	To study efficacy of influenza vaccination in the elderly.	RCS	4B+
KOIVULA [101]	To document risk factors for CAP in the elderly.	PCS	3A+

FARR [102]	To describe prognostic factors in hospitalized CAP.	CCS	4A+
EWIG [103]	To describe risk factors for CAP of unknown aetiology.	PCS	3B+
ANZUETO [105]	To compare ciprofloxacin vs clarithromycin treatment of AECD.	RCT (open)	2C+
BLASI [106]	To document the microbiological aetiology of CAP.	PCS	3A+
BOHTE [107]	To document the microbiological aetiology of hospitalized CAP.	PCS	3A+
BRANDENBURG [108]	To describe the presentation, treatment and outcome of pneumococcal pneumonia.	PCS	3A+
EL SOLH [109]	To describe the aetiology of severe CAP in the elderly.	PCS	3A+
GINESU [110]	To document the microbiological aetiology, risk factors and description of treatments of CAP.	RCS	4B+
GOMEZ [111]	To document the microbiological aetiology and prognostic factors of CAP.	PCS	3B+
HEDLUND [112]	To document the microbiological aetiology and risk factors for recurrent CAP.	PCS	3B+
HIRANI [113]	To study the impact of guidelines on CAP outcome.	PCS	3B+
JONES [114]	To document the microbiological aetiology of hospitalised CAP and antibiotic susceptibility.	PCS	3B+
LOGROSCINO [115]	To describe the presentation, microbiological aetiology, management, outcome of CAP.	PCS	3B+
LORENTE [116]	To study the yield and diagnostic characteristics of PCR to detect pneumococcal infection.	PCS	3B+
LIM [117]	To document the presentation, microbiological aetiology, outcome, prognostic factors of hospitalised CAP.	PCS	3B+
MARRIE [118]	To document the presentation, microbiological aetiology, outcome and prognostic factors of non-hospitalized CAP.	PCS	3B+
MEIJER [119]	To document the microbiological aetiology of LRTIs in general practice: viruses and atypical pathogens.	PCS+CCS	3B+
MENENDEZ [120]	To study the yield of PCR for diagnosis of atypical pathogens and <i>S. pneumoniae</i> in CAP.	PCS	3B+

MICHETTI [121]	To document the presentation, microbiological aetiology, treatment and outcome of CAP.	PCS	3B+
OLAECHEA [122]	To study prediction of pathogens involved in CAP requiring ICU admission.	PCS	3B+
RUIZ [123]	To identify factors associated with microbiological aetiology of CAP.	PCS	3B+
SOCAN [124]	To identify microbiological aetiology of hospitalised CAP.	PCS	3B+
SOPENA [125]	To describe the microbiological aetiology of CAP.	PCS	3B+
STEINHOFF [126]	To document the incidence of CAP due to <i>C. pneumoniae</i> .	PCS	3B+
ELLER [127]	To study the aetiology of AECB depending on lung function.	PCS	3B+
MIRAVITLLES [128]	To study the microbiological aetiology according to lung function in AECOPD.	CSS	4B+
LIEBERMAN [129]	To document microbiological aetiology of hospitalized CAP and AECB.	PCS	3B+
BUSCHO [130]	To document microbiological aetiologies of AECB.	PCS	3B+
SETHI [131]	To document microbiological aetiology of AECOPD.	PCS	3A+
ANGRILL [132]	To document microbiology of & risk factors for lower airways colonization in bronchiectasis.	PCS	3A+
HO [133]	To study consequences of colonization/infection with <i>P. aeruginosa</i> in bronchiectasis.	CSS	4B+
EWIG [134]	To document incidence, risk factors, outcome for drug-resistant pneumococcal CAP:.	PCS	3B+
FELMINGHAM [135]	To describe antibiotic susceptibility in LRTI.	PCS	3B+
FELMINGHAM [136]	To describe antibiotic susceptibility in LRTI.	PCS	3B+
GROOM [137]	To identify description and risk factors for MRSA infections.	RCS	4B+
MARCO [138]	To study determinants of pneumococcal susceptibility to antibiotics.	PCS	3B+
MELO-CRISTINO [139]	To study susceptibility to antibiotics of pathogens involved in LRTIs.	RCS	4B+
SCHITO [140]	To describe antibiotic susceptibility in LRTIs.	CSS	4C+
PALLARES [141]	To document risk factors, outcome,	RCS,	4A+

	prognostic factors for Penicillin-resistant pneumococcal bacteremic CAP.	CCS	
PALLARES [142]	To document risk factors, outcome, prognostic factors for penicillin-resistant pneumococcal bacteremic CAP.	PCS, CCS	3A+
FEIKIN [143]	To study effect of antibiotic resistance on mortality from invasive pneumococcal pneumonia.	RCS	4B+
MORONEY [144]	To study effect of antibiotic resistance on outcomes of pneumococcal CAP.	CCS	4B+
AILANI [145]	To perform a medico-economic evaluation of doxycycline for treatment of CAP.	RCT	2A+
FARR [146]	To document risk factors for CAP seen in general practice.	CCS	4B+
LOEB [147]	Risk factors for CAP in nursing home residents.	PCS	3B+
NIEDERMAN [148]	Epidemiology pneumonia in the elderly	MA	6B+
LIM [149]	To describe presentation, microbiological aetiology, outcome of hospitalized CAP: effect of nursing home residency.	PCS	3B+
MARRIE [150]	To describe presentation, microbiological aetiology, outcome and prognostic factors of hospitalized CAP in the elderly.	PCS	3B+
MEHR [151]	To describe outcome and prognostic factors of LRTIs in nursing home residents.	PCS	3B+
MENEC [152]	To study effect of institutionalisation on outcomes of LRTI.	RCS	4B+
WADA [153]	To document risk factors for aspiration pneumonia in Alzheimer's disease.	RCS	4B+
TERPENNING [154]	To document risk factors for aspiration pneumonia in the elderly.	PCS	3B+
OSTERWEIL [155]	To describe aetiology and outcome of a LRTI outbreak in a nursing home.	RCS	4B+
FINE [156]	To identify prognostic factors in CAP.	PCS	3B+
BARKER [157]	To document influenza-related mortality.	RCS	4B+
LANGE [158]	To document outcome and prognostic factors of hospitalised	PCS	3B+

	CAP.		
MUDER [159]	To document outcome and recurrence of CAP in nursing home residents and their determinants.	PCS	3B+
LIPSKY [160]	To describe risk factors for pneumococcal infection.	RCS, CCS	4B+
GILBERT [161]	To study prognosis in community-acquired pneumonia	MA	6B+
VENKATESAN [162]	To document presentation, microbiological aetiology, outcome and prognostic factors CAP in the elderly:.	PCS	3B+
EBRIGHT [163]	To describe epidemiology of CAP in the elderly.	RCS	4C+
GARB [164]	To describe microbiological aetiology of CAP in nursing homes and community	CCS	4B+
VALENTI [165]	To identify risk factors for oropharyngeal colonization in the elderly.	CSS	4B+
PALMER [166]	To identify risk factors for oral bacteremic colonization.	PCS	3A+
MARRIE [167]	To describe presentation, microbiological aetiology, outcome and prognostic factors of hospitalized CAP.	PCS	3B+
FINE [168]	To identify prognostic factors in CAP.	PCS	3B+
LEVY [169]	To study yield of a non-invasive diagnostic strategy in CAP.	PCS	3B+
ORTQVIST [170]	To determine the microbiological aetiology, outcome and prognostic factors of hospitalised CAP.	PCS	3B+
WOODHEAD [171]	To determine the microbiological aetiology, outcome and prognostic factors of severe CAP.	RCS	4B+
PACHON [172]	To determine the microbiological aetiology, outcome, prognostic factors and management of severe CAP.	PCS	3B+
British Thoracic Society Research Committee and The Public Health Laboratory Service. [173]	To determine the aetiology, management and outcome of severe community- acquired pneumonia on the intensive care unit.	RCS	4B+
DAHMAH [174]	To determine the etiology of CAP in the ICU.	PCS	3B+
MOINE [175]	To describe the presentation, microbiological aetiology,	PCS	3B+

	management and outcome of severe CAP requiring ICU admission.		
FERNANDEZ-SOLA [176]	To study the effect of Alcohol intake on CAP (incidence and outcome).	CCS, PCS	3B+
RUIZ [177]	To determine risk factors for and outcome of severe CAP.	CCS	4B+
ORTQVIST [178]	To describe the outcome of bacteremic vs non –bacteremic CAP.	RCS	4B+
PERLINO [179]	To determine risk factors for pneumococcal infection.	RCS	4B+
TORRES [180]	To determine the microbiological aetiology, outcome and prognostic factors of severe CAP.	RCS	4B+
SULLIVAN [181]	To determine the microbiological aetiology and risk factors for hospitalised CAP.	PCS	3B+
DORFF [182]	To describe the presentation and aetiology of hospitalized CAP.	PCS	3B+
MOORE [183]	To describe population characteristics, admission diagnoses, causative pathogens, frequency of associated illnesses, antibiotic usage and mortality of CAP.	RCS	4B+
DAVIS [184]	To describe the epidemiology of Legionnaire’s Disease	MA	6B+
FALCO [185]	To document the presentation and outcome of CAP due to <i>L. Pneumophila</i> .	PCS	3B+
NIEDERMAN. [186]	To study the effect of malnutrition on the pathogenesis and prevention of pneumonia	MA	6B+
BAIK [187]	To determine risk factors for CAP.	CCS	3A+
Brown K.H., [188]	To study the influence of malnutrition on oropharyngeal bacterial colonisation	CCS	4B+
MULLEN [189]	To determine the prognostic implications of nutritional parameters in surgical patients.	PCS	3B+
NWILOH [190]	To study outcome of surgically-treated pleuro-pulmonary suppurations.	RCS	4C+
The British Thoracic Society and the Public Health Laboratory Service.[191]	To document the epidemiology of hospitalized CAP.	PCS	3A+
KARK [192]	To determine the risk factors for	RCS	4B+

	influenza (cigarette smoking).		
ALMIRALL [193]	To determine risk factors for CAP.	CCS	4A+
NUORTI [194]	To determine risk factors for invasive pneumococcal disease: cigarette smoking.		
HOUSTON [195]	To study prognostic factors of LRTI in the elderly.	RCS	4B+
AKBAR [196]	To compare microbiology and outcome of CAP between diabetics and non-diabetics.	CCS	4A+
FANG [197]	To determine microbiological aetiology of CAP.	PCS	3B+
ARANCIBIA [198]	To study the incidence, risk factors and prognosis of CAP due to gram-negative bacilli:	PCS	3A+
COGGON [199]	To study welding as a risk factor for CAP.	RCS	4B+
AUSTRIAN [200]	To study the efficacy of anti-pneumococcal vaccine.	RCT	2A+
BENIN [201]	To determine risk of <i>L. Pneumophila</i> infection after exposure.	PCS	3A+
BENKEL [202]	To describe a <i>L. pneumophila</i> outbreak+case-control & cohort study.	RCS, CCS, PCS	3A+
BROWN [203]	To describe investigation of a <i>L. Pneumophila</i> outbreak.	PCS	3B+
JERNIGAN [204]	To describe a <i>L. pneumophila</i> outbreak+case-control & cohort study.	RCS, CCS, PCS	3A+
KELLER [205]	To describe a <i>L. pneumophila</i> outbreak+case-control & cohort study.	RCS, CCS,	4A+
NAVA [206]	To determine risk factors for CAP due to resistant <i>S. pneumoniae</i> .	PCS+CCS	3B+
NUORTI [207]	To describe an outbreak of CAP due to resistant <i>S. pneumoniae</i> in nursing home residents, risk factors.	RCS	4A+
JOHANSON [208]	To document bacterial pharyngeal flora.	PCS	3B+
KETAI [209]	To determine outcomes associated with oropharyngeal bacterial colonization after mechanical ventilation.	PCS	3B+
ESPOSITO [210]	To study effect of age on presentation and outcome of pneumococcal pneumonia.	PCS	3B+
BOLDY [15]	To study the presentation and etiology of acute bronchitis.	PCS	3B+
EVERETT [50]	To document the aetiology of lower	CCS	4B+

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	respiratory tract infection in the community		
FRANSEN [211]	To describe the microbiological aetiology of LRTI	RCS	4B+
MARDH [212]	To study the epidemiology of LRTIs in general practice: incidence, microbiological aetiology, role of <i>M. Pneumoniae</i> .	PCS	3C+
SHAW [49]	To study the presentation of LRTIs in general practice.	PCS	3B+
BERNTSSON [213]	To describe the microbiological aetiology of non-hospitalized CAP.	RCS	4A+
BLANQUER [214]	To describe the microbiological aetiology of hospitalized CAP.	PCS	3A+
DULAKE [215]	To document the incidence of CAP.	PCS	3B+
FOY [216]	To document the microbiological aetiology of CAP (viruses, Mycoplasma).	PCS	3B+
MELBYE [45]	To study presentation and microbiological aetiology of CAP in general practice.	PCS	3B+
AUBERTIN [217]	To describe incidence of <i>L. pneumophila</i> infection among patients with CAP.	PCS	3B+
AUSINA [218]	To determine microbiological etiologies of CAP.	PCS	3B+
BERNTSSON [219]	To describe microbiological aetiology of hospitalized CAP.	RCS	4A+
BURMAN [220]	To determine etiology of CAP and diagnosis of pneumococcal pneumonia.	PCS	3A+
HOLMBERG [221]	To determine microbiological aetiology of hospitalised CAP.	PCS	3B+
HONE [222]	To determine microbiological aetiology of CAP ( <i>L. pneumophila</i> ).	CSS	4B+
MACFARLANE [223]	To describe the incidence, microbiological aetiology, outcome and prognostic factors of hospitalized CAP.	PCS	3B+
MCNABB [224]	To determine microbiological aetiology of hospitalized CAP.	PCS	3B+
OSTERGAARD [225]	To determine microbiological aetiology of CAP.	RCS	4B+
PAREJA [226]	To determine microbiological aetiology of CAP.	PCS	3B+
RUF [227]	To describe incidence of <i>L. pneumophila</i> among patients with hospitalised CAP.	PCS	3B+
WHITE [228]	To determine microbiological aetiology of CAP.	PCS	3B+

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ALKHAYER [229]	To study outcome of severe CAP admitted to the ICU.	PCS	3C+
LEROY [230]	To document presentation, microbiological aetiology, treatment, outcome, prognostic factors of CAP requiring ICU admission.	RCS	4B+
ORTQVIST [231]	To determine risk factors for and prognostic factors of CAP requiring ICU admission.	RCS	4B+
RELLO [232]	To determine microbiological aetiology and outcome of severe CAP.	PCS	3B+
SORENSEN [233]	To evaluate a diagnostic strategy in CAP.	PCS	3B+
BEATY [234]	To describe the incidence of <i>C. pneumoniae</i> infection among COPD patients.	PCS	3B+
CARILLI [235]	To study viruses in CB.	PCS	3B+
EADIE [236]	To study viruses as causes of AECB.	PCS	3B+
FAGON [237]	To determine microbiological aetiology of severe AECB.	PCS	3A+
GUMP [238]	To determine microbiological aetiology of AECB.	PCS	3B+
KARNAK [239]	To investigate role of <i>C. pneumoniae</i> infection in AECOPD.	CCS	4B+
LAMY [240]	To determine microbiological aetiology of AECB (viruses).	PCS	3B+
LIEBERMAN [241]	To determine microbiological aetiology of hospitalized AECOPD: role of <i>C. pneumoniae</i> .	PCS	3B+
MCNAMARA [242]	To determine microbiological aetiology of exacerbations of chronic lung disease.	PCS	3B+
MOGULKOC [243]	To determine microbiological aetiology of AECOPD, role of <i>C. pneumoniae</i> .	PCS	3B+
MONSÒ [244]	To determine microbiological aetiology of AECOPD.	CCS	4A+
ROSS [245]	To determine microbiological aetiology of AECB.	PCS	3B+
SEEMUNGAL [246]	To describe presentation and microbiological aetiology of AECOPD.	PCS	3B+
SOLER [247]	To determine microbiological aetiology of severe AECOPD.	PCS	3B+
CHAN [248]	To study treatment of exacerbations of bronchiectasis: ciprofloxacin vs amoxicillin.	RCT	2B+

O'DONNELL [249]	To study effect of RhDNAse in bronchiectasis.	RCT	2B+
FELMINGHAM [250]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
OTEO [251]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
ROUSSEL-DELVALLEZ[252]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
VANHOOF [253]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
MARAKI [254]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
TARASI [255]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
REINERT [256]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
MELO-CRISTINO[139]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
DE NEELING[257]	To study antibiotic resistance in <i>S pneumoniae</i>	PCS	4B+
WOODHEAD [258]	To describe presentation of CAP depending on aetiology.	RCS	4B+

Similarly, the proportion of beta-lactamase positive *H. influenzae* varies from 2% to 22% in Europe [140]. Resistance of this pathogen to beta-lactams in the absence of beta-lactamase production occurs in less than 1% in most studies.

Production of beta-lactams by *M. catarrhalis* is much more frequent (82–94%) [135, 139, 140].

Most of the above-mentioned variations between areas can be attributed to local habits in the use of antibiotics, inducing different selection pressures; these variations make it mandatory to take into account local resistance profiles when developing and implementing guidelines on antibiotic strategies.

The impact of antibiotic resistance in community-acquired LRTI and CAP has been studied mostly for *S. pneumoniae*. A retrospective case-control study of 72 patients in Spain found no response to beta-lactams in two patients with infections due to *S pneumoniae* with MICs of 4 and 8  $\mu\text{g}\cdot\text{l}^{-1}$ , respectively [141]. In a subsequent 10-year prospective study conducted by the same team, resistance or decreased sensibility of this pathogen to penicillin and cephalosporin were not associated with an increased mortality in 204 patients with pneumococcal pneumonia (including 145 patients with penicillin-resistant strains and 31 with cephalosporin-resistant strains) [142]. Similar results have been provided by three other studies in 5837, 146 and 101 patients, respectively [134, 143, 144]. However, in the large study by FEIKIN *et al.* (n=5837 invasive pneumococcal pneumonia, 12% mortality rate), mortality after day 4 was higher in patients with penicillin MIC $>$ 4  $\mu\text{g}\cdot\text{l}^{-1}$  or cephalosporin MIC $>$ 2  $\mu\text{g}\cdot\text{l}^{-1}$  [143]. Finally, a retrospective case-control study found a longer delay before response to

treatment and an increased hospital length of stay in patients with CAP due *S. pneumoniae* with high levels of cephalosporin-resistance [145]. So current levels of resistance of *S. pneumoniae* do not appear to impact significantly on the outcome of CAP due to *S. pneumoniae*. However, high levels of resistance to penicillin and cephalosporins may increase mortality after day 4, time-to-response and length of stay. The clinical impact of macrolide and tetracycline resistance is unclear.

### ***Risk factors for the occurrence of lower respiratory tract infection***

The respiratory tract has a system of defence that enables the lower respiratory tract to remain sterile. Infection develops when the microbial clearance system is overwhelmed. This is controlled by three factors: the virulence of the infecting agent, the volume of the inoculum and the host, *i.e.* intrinsic factors likely to decrease anti-infectious defences such as immunity failure or defective phagocytosis. Virulence will explain the occurrence of LRTI in healthy subjects and its possible severity, even in the absence of risk factors.

Three types of risk factors can be distinguished: (1) factors predisposing to the occurrence of bronchopulmonary infection; the identification of which will facilitate prevention; (2) factors predisposing to infection severity which will permit assessment of the need for hospitalisation; (3) factors controlling infection by specific, opportunist or unusual micro-organisms. These distinctions, although useful for didactic purposes, are somehow academic, because the various risk factors most usually occur together. Most studies focused on risk factors for pneumonia (rather than LRTI) occurrence and severity, and for LRTI or pneumonia-related death. The distribution of involved pathogens according to underlying risk factors has also been addressed in several studies.

### **Ageing and institutionalisation**

The 65 years threshold is arbitrary: ageing is a physiological phenomenon, which begins early in life, and is characterised by a progressive functional involution which differs with organs and other factors such as genetics, environmental exposure, malnutrition and alcoholism, associated chronic diseases, long duration cures, and way of life. So age as an independent risk factor is a complex topic as likelihood of other risk factors will increase with increasing age, including institutionalisation and co-morbidities. Moreover, the relevance of this threshold is discussed as life expectancy without any handicap increases and more advanced age - over 75–80 years - represents a risk factor in itself which is likely more significant.

In most studies carried out, age is a major risk factor for both occurrence and severity of pneumonia [1, 80, 84, 89, 90, 94, 97, 99, 101, 112, 143, 146, 147]. MACFARLANE *et al.* have studied adults presenting to a single general practice with community-acquired LRTI; the incidence was 2–4 times higher in people aged 60 and over than in those aged less than 50[27]. The annual incidence of pneumonia in non-institutionalised elderly people is not known precisely, varying between 19 and 44/1000, compared with 4.7 and 11.6/1000 in the general population [42, 74, 77, 79, 148]. In Koivula's study [101], age was a relative risk factor with each year over 65 increasing the risk of contracting pneumonia by a factor of 1.07.

The risk of pneumonia increases in institutionalised patients. Nursing-home acquired pneumonia is an important cause of morbidity, mortality, and hospitalisation [147,

149–152]. LOEB *et al.* found a relative risk of 1.7 per 10 years of age in institutionalised patients, risk factors for pneumonia occurrence being swallowing difficulties, inability to take oral medications, immobility and male gender [147]. Aspiration pneumonia appears to be more frequent in patients with a more severe dementia or taking neuroleptics [147, 153], or in elderly people with COPD, diabetes mellitus or poor dental status [154]. Epidemics of viral infections, often severe, are particularly frequent in institutionalised patients [155], particularly with the lack of influenza vaccination [147].

Hospitalisations as a result of severity of CAP increase significantly with age, ranging from 1.6/1000 between 55 and 64 to 11.6/1000 after 75 [150]. As a result, about one half of hospitalisations for pneumonia occur in patients aged 65 years or more [80]. Correspondingly, hospitalisation for LRTI in subjects older than 79 years (30/1000/year) is 20 times higher than in the 16–40 age range (1.5/1000/year) [84].

Mortality due to pneumonia and/or *influenza* has been evaluated at 9/100,000 in the elderly, reaching 217/100,000 in patients with one associated risk factor and 979/100,000 in those with more than one [148]. FINE *et al.* evaluated the relative risk of death in people with pneumonia aged more than 65 years at 2.1 in a study of 14 199 patients [156]. This higher mortality is mainly associated with coexisting heart failure, cerebral vascular disease, cancer, diabetes mellitus or COPD [112, 143, 157, 158]. Among institutionalised patients, the relative risk of dying because of pneumonia was increased to 9 [101]. As expected, the long-term prognosis after a pneumonia in people living in a nursing home depends mainly on their general health status, as reflected by measurements such as the activity of daily living scale [149, 159].

*S. pneumoniae* is the most frequent microbial agent to be found in bacteriologically documented pneumonia in both elderly and middle aged adults. The risk of pneumonia due to *S. pneumoniae* is higher in old people than in the general population [97]. In Lipsky's study, the occurrence of pneumonia due to *S. pneumoniae* was 3 times more frequent in institutionalised patients than in non-institutionalised subjects of the same age, and the relative risk of pneumococcal infection increased linearly with age, from 1.63 between 61 and 70 years, to 3.60 over 80 years [160].

Higher frequency of GNEB, *Staph. aureus* and anaerobic bacteria have been reported in the elderly, with an increased risk of death, *i.e.* 59% for *Staph. aureus* and 33% for GNEB [161]. If the presence of these micro-organisms in active and ambulatory elderly people does not, however, appear to differ significantly from that observed in adults below 65 years old [162], it does in seriously disabled, institutionalised or hospitalised patients [109, 163, 164]. El Sohl reported a frequency of 30% *Staph. aureus* and 4% *P. aeruginosa* pneumonia in institutionalised patients [109].

Previous oro-pharyngeal colonisation by GNEB or *Staph. aureus* probably plays a major role in institutionalised patients, as contamination of the lower respiratory tract is mainly due to micro-aspiration. VALENTI *et al.* [165] demonstrated that oro-pharyngeal colonisation by GNEB was more frequent in institutionalised or hospitalised elderly people, colonisation related to a decrease in salivary clearance of bacteria [166].

## Alcoholism

Alcohol has numerous deleterious effects on respiratory tract defences. These include alteration in coughing reflexes, swallowing and mucociliary transport, facilitation of bacterial colonisation of the oropharynx by Gram-negative bacilli and alteration of the functions of various cells which play a role in specific and non-specific defences *i.e.* lymphocytes, neutrophils, monocytes, and alveolar macrophages. Such alterations explain the reduced bacterial clearance of the airways observed in experimental animal models.

In pneumonia, there is a large variation - 6 to 37% - in the proportion of alcoholic patients [167–175]. Data are conflicting about the risk for occurrence and severity for pneumonia in case of excessive alcohol intake.

It is reported as increasing the risk for pneumonia, severe pneumonia, death from pneumonia and GNEB-related pneumonia [101, 176, 177], particularly the risk for pneumonia in people aged 60 years or more which is increased by a factor of 9 [101]. Bacteraemia seemed to be more frequently associated with alcoholism [178]. And Perlino and Rimland characterised a syndrome associating alcoholism, leucopenia and pneumococcal sepsis in young subjects, that was correlated with a considerable increase in mortality [179]. In other studies, alcohol did not influence either the severity or mortality of LRTIs [167–172, 174, 175, 180].

Although *S. pneumoniae* may be associated with an increase in mortality, *S. pneumoniae* or *H. influenzae* do not appear to be more frequent in pneumonias in alcoholic patients than in the general population [160, 167–172, 174, 175, 180]. The prevalence of alcoholic subjects was high in series of pneumonias in which the proportion of GNEB infections was increased [181–183]; but as these studies are relatively old, the validity of the techniques used for microbiological identification remains debatable. A high frequency of alcoholism was detected in patients infected by *L. pneumophila* [184, 185]. Alcoholism was found in 60% of patients presenting with pneumonia due to *L. pneumophila* compared with 26.2% of patients presenting a pneumococcal pneumonia in Falco's study [185]; however, patients were often smokers which also predisposes to infection with *L. pneumophila* [184].

Thus alcoholism would appear to be a risk factor, particularly in old subjects but would not be associated with poorer prognosis, except in the case of pneumococcal infection with leucopenia. Infection with GNEB and *L. pneumophila* would seem to occur more frequently in alcoholics.

## Nutrition

Malnutrition has multiple effects on airway defences, with three types of consequences: 1) an increase in the incidence of respiratory infections; 2) a greater severity of such infections and 3) an often "atypical" clinical presentation [186].

Obesity and malnutrition increase the risk of developing LRTI. Obesity increased the risk of CAP by a factor 2 in adults with an increase of 40 lbs in body weight [187]. BROWN *et al.* in Bangladesh suitably demonstrated the role of malnutrition as a risk factor for pneumonia in children [188]. Nutritional data from adults have rarely been

analysed individually in published series, as they usually act in association with other factors of co-morbidity such as alcohol consumption or COPD. MULLEN *et al.* observed a significant increase in the risk of postoperative infection, and especially of LRTI in patients initially presenting with criteria of malnutrition [189]. In addition, nutritional status reduces prognosis of infections. Poor nutritional status was associated with an increase in mortality in a Bangladesh study [188]. In patients with a suppurative respiratory disease requiring surgery, postoperative mortality closely correlated with malnutrition as measured by blood albumin and delayed hypersensitivity to microbial antigens [190].

### Smoking

The effects of tobacco smoke on the airway mucosa are well known. The chronic inhalation of smoke favours the adhesion of *S. pneumoniae* and *H. influenzae* to the buccal epithelium. Smoking alters mucociliary transport, humoral and cellular defences, and epithelial cells. The proportion of smokers in hospitalised pneumonias is generally increased, which would indicate a role of smoking in the acquisition of infection. It is however difficult to distinguish between the role of smoking and that of COPD, which is often present in these patients. Thus the study by Ortqvist [170] included 37% smokers and 19% “respiratory diseases”; that of Fine [168] 34% of smokers and 15% of COPD, whereas 46% of smokers and 39% of COPD were mentioned in the British study carried out in 1987 [191]. Smoking does not appear to be a factor of increased mortality in the case of pneumonia. None of the above-cited studies demonstrated any such association. On the other hand, smoking does seem to predispose to infection with certain micro-organisms. Thus *influenza* infection appears more frequently in smokers [192]. The risk of infection by *L. pneumophila* is also increased [184, 185]; 60% of patients infected by this germ were smokers in the series described by Falco [185]. Lipsky identified smoking as a very significant risk factor in *S. pneumoniae* pneumonia, with a relative risk of 4.5 in smokers smoking more than one pack per day and of 3.53 in others [160]. The risk in previous smokers is not significantly increased. Other studies found risk ratios of about 1.5 in all smokers [187] and 2.8 in smokers of more than one pack per day [193]. NUORTI *et al.* showed that cigarette smoking was the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults [194]. Invasive pneumococcal disease was associated with cigarette smoking (odds ratio, 4.1) and with passive smoking among non-smokers (odds ratio, 2.5) after adjustment. There were dose-response relations for the current number of cigarettes smoked per day, pack-years of smoking, and time since quitting. The adjusted population attributable risk was 51 percent for cigarette smoking, 17 percent for passive smoking, and 14 percent for chronic illness.

### Associated diseases

Co-morbidities are frequent among patients hospitalised for pneumonia [167–172, 174, 175, 180], ranging from 46.2% in the study by PACHON *et al.* [172] to 80% in the study by FINE *et al.* [168]. According to KOIVULA *et al.*, the relative risk of pneumonia is 2 for a cardiac disease, 3 for a pulmonary disease (and 4 for asthma) [101]. Two studies, one in 170 patients [168] and the other in 14,199 patients from 78 hospitals [156] demonstrate an increase in severity related to the addition of co-morbidity to age and to a high risk aetiology. Increase in mortality might be credited to co-morbidities. For example, in one study, 71.4% of deceased patients had a factor of co-morbidity compared with 39.6% in the survivors [172]; and there are various

studies which report increase mortality associated with pneumonia in specific comorbidities.

The most frequent co-morbidity is COPD which is reported in 13 to 53% of the cases; and the rate of hospitalisation for pneumonia correlated with FEV<sub>1</sub> in a study [158]. The risk of death due to pneumonia when the FEV<sub>1</sub> was lower than 60% of the predicted value was increased by 5.7 in females and by 2.3 in males [158]. Cardiovascular diseases might be frequent: 25% in the study by MARRIE *et al.* [167] and 30% in the study by FINE *et al.* [168]. Their incidence was much lower in the British hospital study [191] and in the study by ORTQVIST *et al.* [170] (11 and 6% respectively) and only 3% in the Dahmash series [174]. In the study by KOIVULA *et al.*, the risk of death was multiplied by 5 in case of associated cardiac disease [101]. Neurological diseases range from 5% in the British hospitals patients [191] to 24% in the Marrie's study [167], the most frequent in very old subjects [167]. Diabetes mellitus ranging from 5% [191] to 16% in the series by TORRES *et al.* [180] that focused on severe pneumonia. Diabetes mellitus indeed appears to increase the risk of death from pneumonia or flu. Some studies also identified an increased risk of death from LRTI in elderly subjects with cancer (OR: 6.2) or neurological diseases (OR: 3.9) [195].

With the exception of conditions of proven immuno-suppression (hypogammaglobulinemia and, hyposplenism favouring pneumococcal bacteraemia, HIV infection with moderate fall in CD4 favouring pneumonia due to *S. pneumoniae* and/or *H. influenzae*), the tropism of a particular micro-organism for a given factor of co-morbidity has not been well established. Pneumonia caused by Gram-positive bacteria (*S. pneumoniae*, *Staph. aureus*) and *H. influenzae* may occur after a viral infection, especially if due to *influenza* [89]. Such bacterial infections are also favoured by COPD, neurological diseases, and diabetes mellitus [160, 196]. Comorbidity factors favour the occurrence of pneumonia due to GNEB [197, 198]. In the study by ELLER *et al.* on exacerbations of COPD, a decrease in FEV<sub>1</sub> was related to an increase in the frequency of GNEB [127] (figure 3).

#### Environmental factors

Environmental factors may favour the occurrence of CAP due to particular micro-organisms.

An increased frequency of pneumonia due to *S. pneumoniae* has been described in soldiers (12/1000), painters (42/1000), welders [199] and in South African gold miners [200]. Legionnaires' disease can occur in subjects exposed to stagnant waters or to domestic water supply systems (hot water reservoirs, taps and shower hot water, humidifiers, air conditioning devices, cooling towers and aerocondensers, spas) [201–205].

Previous hospitalisation considerably increases the risk of pneumonia due to *S. pneumoniae*; the risk is multiplied by 4 in the case of one hospitalisation within the year and by 13 after several [160]. The risk of pneumonia due to penicillin-resistant *S. pneumoniae* after a recent hospitalisation was first shown in 1987 [141], and further demonstrated by univariate analysis in another study [206]. Clusters of penicillin-resistant *S. pneumoniae* infections have been recently reported in nursing homes [207].

Hospitalisation may also be associated with frequent colonisation of the upper respiratory tract by nosocomial bacteria, especially GNEB [208]. The risk of pneumonia due to GNEB is 3.5 times higher in case of hospital admission and 2 times higher in case of antibiotic treatment during the 30 days preceding the occurrence of CAP requiring hospitalisation [198]. The duration of carriage of these bacteria after hospital stay is 2 to 4 weeks, thus leading to pneumonia due to multiresistant bacteria of nosocomial origin [209].

Medications, apart from immunosuppressants, are rarely cited as a risk factor. They may have a role in elderly people, especially when associated with other factors. Thus morphine and atropine interfere with microbial mucociliary clearance; sedatives alter coughing and the epiglottic function of mechanical defence, while corticosteroids and the salicylates act on phagocytosis. Esposito observed that 39% of elderly people with pneumococcal bacteraemia had taken aspirin before the onset of their infection [210]. The use of corticosteroids was associated with a relative risk of pneumococcal pulmonary infection of 1.81 (0.81–4.04) [160]. A recent study has confirmed, in a multivariate analysis, that the risk of pneumonia due to highly penicillin-resistant *S. pneumoniae* is correlated with previous prescriptions of betalactam antibiotics [206].

### **APPENDIX 3. PHARMACODYNAMICS AND PHARMACOKINETICS OF CHEMOTHERAPEUTIC ANTIMICROBIALS: INDICATIONS FOR APPROPRIATE CHOICE AND DOSE REGIMENS**

In the field of antimicrobial chemotherapy, the last years have brought about a critical analysis of the rules dictating both the choice of antimicrobials and their optimal regimen. The aim was to increase the efficacy of antibacterial therapy and reduce the risk of selecting multi-resistant pathogens.

The fundamental criteria for the rational choice of an antimicrobial agent are the knowledge of its pharmacodynamic characteristics, including antimicrobial activity spectrum, type of bactericidal activity, and antibacterial potency. Antimicrobial potency towards pathogens is indicated by the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC). These determine the minimal concentrations capable of exerting antibacterial effects. Analysis of antimicrobial bactericidal activity indicates that there are two prevailing behaviours: for antibiotics such as fluoroquinolones, aminoglycosides, metronidazole, quinopristin-dalfopristin, clarithromycin, azalides, and ketolides there is a direct correlation between bactericidal effect and obtaining high concentrations, even though these are maintained for relatively short periods of time. These antibiotics may therefore be classified as concentration-dependent. From a clinical standpoint, concentration-dependent antibiotics may be administered as high concentration once/twice daily doses in order to obtain bacterial eradication [259]

Conversely, penicillins, cephalosporins, monobactams, oxazolidinones, glycopeptides, and erythromycin, once they have reached adequate concentrations, exert their bactericidal activity on the basis of time span during which the antibiotic is in contact with the microorganism: efficacy is described as time-dependent. In this case, antibiotic administration is best repeated several times during the day so as to obtain optimal bactericidal activity.

Antimicrobial activity may persist after the antibiotic concentration decreases or disappears. This indicates the presence of a post-antibiotic effect (PAE) or a post-antibiotic effect at sub-inhibitory concentrations (PA-SME), or a boost of leukocyte phagocytosis during PAE (PALE). Significant PAE has been described for carbapenems, glycopeptides, macrolides, azalides, ketolides, aminoglycosides, and fluoroquinolones [260].

One of the main goals in treating infections is that within the infected tissue, antibiotic penetration exceeds the minimal inhibitory concentration for the involved pathogen. This constitutes the basic pharmacokinetic criterion in choosing an antibiotic, and is of paramount importance in obtaining pathogen eradication [261–263].

It has been clearly shown that antibiotic serum concentration (and, as a result, infected tissue antibiotic concentration) influences intensity and duration of the antimicrobial effect. This factor, coupled with the minimal inhibitory concentration (the fundamental pharmacodynamic parameter) constitutes a prediction criterion for the clinical efficacy of an antimicrobial agent.

Over the last years, prediction indexes of antibacterial efficacy and antibiotic dose optimisation have been validated both in experimental animals and in man, based on the correlation between pharmacokinetic and pharmacodynamic parameters. The degree of correlation varies for different antibiotic classes, and even for different agents within a single class.

These indexes include: the amount of time with serum concentrations above MIC ( $T > MIC$ ); the ratio between peak concentration ( $C_{max}$ ) and MIC ( $C_{max}/MIC$ ); and the correlation between the area under the curve of serum concentrations over 24 hours ( $AUC_{24}$ ) and MIC ( $AUC_{24}/MIC$ ).

Clinical and bacteriological efficacy of time-dependent antibiotics such as betalactams and erythromycin has been significantly associated with high values of  $T > MIC$ : these must be above 40–50% of the interval between successive administrations so as to guarantee a high percentage of clinical resolution both in animal infection models and in human acute otitis media, sinusitis and osteomyelitis.

Fluoroquinolones, exhibiting concentration-dependent bactericidal activity, must reach a  $C_{Max}/MIC$  ratio of at least 10–12 to obtain optimal efficacy, or an  $AUC_{24}/MIC$  ratio above 125 to improve clinical remission in severe lower respiratory tract infections. However, recent data indicate that lower values for this ratio ( $AUC/MIC$  ratio in the 30–50 range) are sufficient to obtain bacteriological eradication of *S. pneumoniae* with third generation fluoroquinolones both in animal models and in community acquired lower respiratory tract infections. Schentag warns there may be a risk of selecting resistant microorganisms through the use of low  $AUC/MIC$  values [264–266].

Similarly to fluoroquinolones, in aminoglycoside antibiotic treatment,  $C_{max}/MIC$  values  $\cong 10$  are predictive for clinical and bacteriological efficacy [267]. For glycopeptides an  $AUC/MIC$  trough value  $> 125$  is of great importance [268, 269].

The main pharmacokinetic requisites of the ideal antimicrobial agent are maximal oral bioavailability, sufficiently long half-life, and a high ratio between tissue and serum concentrations. This indicates a satisfactory tissue concentration.

There is now an ample choice of oral and parenteral antibiotics at the clinician's disposal. The choice of the administration route is based on the knowledge of the different pharmacological, anatomical, physiological and pathological factors affecting the drug's bioavailability that is its ability to reach adequate concentrations with the site of infection so as to guarantee clinical efficacy.

Oral administration, in cases where the drug is highly bioavailable, is generally the safest and surest route of administration, both in terms of economical cost and patient acceptability. This is particularly true when, based on serum half-life, drug administration is no more than twice daily. Oral administration is generally indicated in mild to moderately severe infections and in the absence of complications.

The choice of parenteral antibiotic administration is usually based on four factors: reduced gastrointestinal absorption, dysphagia or lack of co-operation (*e.g.* children or elderly patients), absence of orally active antibiotic with equivalent activity, specific infections and severity of the disease.

Reduced gastrointestinal absorption may be due to relatively rare conditions such as gastrectomy or short intestine syndrome, but are more commonly due to symptomatic gastrointestinal disorders.

Oral formulations are as yet unavailable for aminoglycosides, carbapenems, glycopeptides and many cephalosporins. Therefore, when bacterial etiology or clinical conditions indicates these antibiotics as first choice treatment, parenteral administration is required.

Lastly, parenteral antibiotic administration is always required in specific infections where the risk of complications is high, such as osteomyelitis, or endocarditis. In broader terms, parenteral administrations is indicated in severe infections and in compromised hosts, both in the out-patient setting and during hospital admission. This is based on the observation that injected antibiotics obtain high serum and tissue concentrations more rapidly compared to oral administration.

Intramuscular administration, practised much more commonly in Italy than in other European countries, possesses intermediate characteristics between intravenous and oral administration: bioavailability is prompt but not as immediate as for intravenous administration. Absorption of aqueous solution antibiotics is based on their concentration and on blood flow velocity in the site of injection. However, this route of administration may be particularly useful when difficulties are encountered in obtaining an intravenous route (vein identification, maintaining catheter patency, high risk of local infection, etc.) or due to logistical problems.

In terms of antibiotic diffusion within the respiratory tract, the airways may be considered as a "simple" target due to the lack of biological barriers (as opposed to the central nervous system). During acute bacterial infections, the fraction of antibiotic unbound to plasma proteins may reach richly vascularised tissues such as

the respiratory tract by simple diffusion through the capillary bed. Drug-protein binding is an important factor that may therefore condition antibiotic tissue penetration in sites lacking a highly specialised capillary membrane.

Tissue factors influencing antibiotic penetration are dictated by the degree of capillary permeability, degree of vascularisation, and presence of inflammation. Acute inflammation generally favours tissue distribution, whereas chronic infection may bring about tissue alterations by creating pseudobarriers, thereby heavily conditioning antibiotic penetration. Tissue distribution is generally hindered by the presence of fibrosis, granuloma formation bacterial and protein debris, as may occur for example in chronic bronchitis. Tissue antibiotic penetration is influenced by drug class, administration characteristics (oral or parenteral, single or repeat doses), and individual molecular tissue diffusion properties, based on physical-clinical aspects.

In summary, antibiotic administration regimen optimisation (dose, route of administration, time interval between doses) in clinical practice requires a thorough knowledge of the pharmacokinetic and pharmacodynamic properties of each antibiotic class (table 39). Specifically, most betalactams (penicillins, cephalosporins, and monobactams) and oxazolidinones are bactericidal at low concentrations, their activity is time-dependent, and they possess little post-antibiotic effect. A correct dose regimen must therefore guarantee prolonged bacterial exposure to these antibiotics, maintaining serum levels adequately above MIC.

The aim with carbapenems, glycopeptides, and natural macrolides is also a prolonged bacterial exposure time, but given the presence a substantial post-antibiotic effect, serum levels may decrease to below MIC in the time interval between doses.

Conversely, optimal dose regimens for aminoglycosides, fluoroquinolones, quinopristin-dalfopristin, semi-synthetic macrolides, azalides, and ketolides require obtaining maximal concentrations, in that bactericidal activity is directly related to high concentrations and almost all these antibiotics possess a prolonged post-antibiotic effect.

TABLE 39 Correlation between pharmacodynamic and pharmacokinetic properties of different antibiotics

Antibiotic	Pharmacodynamics	Pharmacokinetics (posology)
Penicillin	Bactericidal at low concentrations	Need of prolonged bacterial exposure time
Cephalosporins		
Monobactams		
Oxazolidinones	Low or absent PAE	maintaining serum levels adequately above MIC
Carbapenems	Bactericidal even at low concentrations	Need of prolonged bacterial exposure time. Serum levels may decrease to below MIC in the time interval between doses.
Glycopeptides	Prolonged PAE	
Natural Macrolides		
Aminoglycosides	Bactericidal activity related to $C_{max}$	Need to obtain maximal concentrations
Fluoroquinolones		
Quinupristin-dalfopristin	Prolonged PAE	(high levels of $C_{max} / MIC$ or $AUC/MIC$ )

Antibiotic	Pharmacodynamics	Pharmacokinetics (posology)
Semi-synthetic macrolides Azalides Ketolides		

PAE: Post-antibiotic effect; MIC: minimum inhibitory concentration; Cmax: peak serum concentration; AUC: area under the serum concentration curve.

TABLE 40 Mean concentrations of antibiotics in biological fluid, tissues and cells of respiratory tract. Reproduced from [270] with permission from publisher.

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
Amoxicillin	1.2 <sup>a</sup>	0.6 <sup>a</sup>	0.52 (1g os, sd) <sup>b</sup>	1.6 (750mg os, dr) <sup>c</sup>	2.7 (500mg os, dr)	2.4 (1g os, sd) <sup>b</sup>
Clavulanate	1.75 <sup>a</sup>	1.8 <sup>a</sup>	–	–	1.8 (250mg os, sd)	
Ampicillin	–	–	–	0.6±0.1 <sup>d</sup>	38.6±7.2 <sup>d</sup>	–
Sulbactam	–	–	–	0.3±0.1 <sup>d</sup>	28.1±5.2 <sup>d</sup>	–
Azitrmycin	13.2±0.9 (500mg os, sd+250m g os,dr) <sup>e</sup>	464±65 (500mg os, sd+250mg os, dr) <sup>e</sup>	–	–	–	3.9 (500mg os, sd)
Cefaclor	2.71 (750mg os, dr) <sup>f</sup>	–	0.6 (1g os, sd) <sup>c</sup>	–	7.73 (1g os, dr) <sup>g</sup>	–
Cefazoline	–	–	–	12.9– 21.3 (1– 2g <i>i.v.</i> , sd) <sup>c</sup>	–	–
Cefixime	–	–	0.02–0.05 (200mg os, dr)	–	2.4 (400mg os, dr)	–

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
Cefotaxime	–	–	1.8 (1g <i>i.v.</i> , sd) <sup>b</sup> 1.4 (1g <i>i.m.</i> , sd) <sup>b</sup>	7.2 (1g <i>i.v.</i> , sd)	–	19.5(1g <i>i.v.</i> , sd) <sup>b</sup> 4.8 (1g <i>i.m.</i> , sd) <sup>b</sup>
Cepodoxime proxetil	–	–	–	–	0.9 (200mg os, sd)	–
Ceftazidim <sup>+</sup>	–	–	–	17 (2g <i>i.v.</i> , sd) <sup>c</sup>	–	10 (1g <i>i.v.</i> , sd) <sup>b</sup>
Ceftibuten	1.5 (400mg os, sd)	–	–	–	5.7 (400mg os, sd)	–
Ceftraxon	–	–	1.9 (1–2g <i>i.v.</i> , sd) <sup>b</sup> 2.3 (1g <i>i.m.</i> , sd) <sup>b</sup> 0.4 (1g <i>i.m.</i> , sd) <sup>g</sup>	7.9 (1g <i>i.v.</i> , sd) <sup>c</sup>	–	19.5(1g <i>i.v.</i> , sd) <sup>b</sup> 11.5 (1g <i>i.m.</i> , sd) <sup>b</sup> 3.87 (1g <i>i.v.</i> , sd) <sup>g</sup> 2.18 (1g <i>i.m.</i> , sd) <sup>g</sup>
Cefuroxime axetil	0.7 (500mg os, sd)	–	3.5+1.0 (500mg os, sd)	–	1.8 (500mg os, sd)	–
Ciprofloxacin	–	–	1.3–1.4 (500mg os, sd)	0.4–1.5 (250mg os, sd) 1.2–1.4 (500mg os, sd)	1.0 (250mg os, sd) 1.7–6,9 (500mg os, sd) 1.3–11.0 (200mg <i>i.v.</i> , sd)	1.3–3.0 (250mg os, sd) 2.2–4.5 (500mg os,sd) 2.1–4.7 (200mg os, sd)

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
				os, sd) 1.0–1.8 (200mg <i>i.v.</i> , sd)		<i>i.v.</i> , sd)
Clarithromyci	34.02±5.2 (500mg os, dr) <sup>h</sup>	1996±2539 (500mg os, dr) <sup>h</sup>	2.66 (250mg os, dr)	31.55 (500mg os, dr) <sup>h</sup>	–	28.19(500mg os, dr)
Erythromycin	0 (250os, dr) <sup>i</sup> 0.8 ± 0.1 (250os, dr) <sup>h</sup>	0.1± 0.3 (250os, dr) <sup>i</sup> 0 (250os, dr) <sup>h</sup>	0.59 (1g os, dr)	–	–	4.2 (250 o 500mg os, dr)
Imipenem	–	–	0.6 +2.1 (1g <i>i.v.</i> , sd) <sup>l</sup> 0.94+0.12 (1g <i>i.v.</i> , sd) <sup>l</sup>	–	–	12 (1g <i>i.v.</i> , sd) <sup>c</sup>
Levofloxacin	9.0 (500mg os, sd) <sup>m</sup>	41.9 (500mg os, sd) <sup>m</sup>	–	–	–	7.74 (500mg os, sd)
Linezolid	64.3±33.1 (600mg os, sd) <sup>h</sup>	2.2±0.6 (600mg os, sd) <sup>h</sup>	–	–	–	–

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
Meropenem	–	–	0.46 (1g <i>i.v.</i> , sd) <sup>l</sup> 0.24 (1g <i>i.v.</i> , sd) <sup>n</sup> 0.53 (1g <i>i.v.</i> , sd) <sup>o</sup>	2.29 (1g <i>i.v.</i> , sd) <sup>l</sup> 0.62 (1g <i>v.</i> , sd) <sup>n</sup> 1.72 (1g <i>i.v.</i> , sd) <sup>o</sup>	4.53 (1g <i>i.v.</i> , sd) <sup>t</sup> 0.08 (1g <i>i.v.</i> , sd) <sup>m</sup> 1.81 (1g <i>i.v.</i> , sd) <sup>n</sup>	2.86 (1g <i>i.v.</i> , sd) <sup>t</sup> 4.83 (1g <i>i.v.</i> , sd) <sup>m</sup> 3.29 (1g <i>i.v.</i> , sd) <sup>n</sup>
Moxifloxacin	22.4 (500mg os, sd)	113.6 (500mg os, sd)	–	–	5.5 (500mg os, sd)	–
Piperacillin	–	–	29.3 <sup>p</sup> 20.2 <sup>q</sup>	–	162 <sup>p</sup> 9.7 <sup>q</sup>	67.1 <sup>p</sup> 1.2 <sup>q</sup>
Tazobactam	–	–	6.86 <sup>p</sup> 4.25 <sup>q</sup>	–	23.7 <sup>p</sup> 1.76 <sup>q</sup>	14.2 <sup>p</sup> 0.74 <sup>q</sup>
Teicoplanin	–	–	–	2.8 (400 mg·kg <sup>-1</sup> <i>i.v.</i> , sd)	–	14 (400 mg·kg <sup>-1</sup> <i>i.v.</i> , sd)
Telithromycin	14 (800mg os, sd) <sup>n</sup>	70 (800mg os, sd) <sup>n</sup>	–	–	4 (800mg os, sd) <sup>n</sup>	–
Tobramycin	5.3–5.5 (300mg <i>i.m.</i> sd·md <sup>-1</sup> ) <sup>r</sup>	3.0–3.3 (300mg <i>i.m.</i> sd·md <sup>-1</sup> ) <sup>r</sup>	–	–	–	–
Vancomycin	0.4–8.1 (15	–	–	2.9 (500mg	–	–

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
	mg·kg <sup>-1</sup> <i>i.v.</i> , md)			<i>i.v.</i> , sd)		

sd: single dose; md: multiple dose; os: oral; *i.v.*: intravenous; *i.m.*: intramuscular; -: no data. a: 750mg Amoxi-clav (4:1); b: 1-3 h from administration; c: 2-4 h from administration; d: after 30 min one *i.v.* dose of ampicillin/sulbactam 2g/1g; e: 5 days from administration; f: 32-48 h from administration; g: 24 h from administration; h: 4 h from administration; i: 8 h from administration; l: 1 h from administration; m: 2-3 h from administration; n: 2 h from administration; o: 3 h from administration; p: after a 4/0.5g dose (*i.v.*, multiple dose), 30' from last administration; q: after a 4/0.5g dose (*i.v.*, multiple dose), 6 h from last administration; r: 6 h from administration.

TABLE 41 Main pharmacokinetics parameters of oral and parenteral penicillins , and suggested dosing. Reproduced from [271–275] with permission from publisher.

Antibiotic	Biodisposability (%)	T <sub>max</sub> (h)	C <sub>max</sub> (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	V <sub>d</sub> (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Urinary clearance (%)	Dose
Amoxicillin	93±10 <sup>a</sup>	1–2	<i>i.v.</i> : 46±12 <sup>b</sup> os: 5 <sup>b</sup>	18	1.7±0.3 ↔ children	0.21±0.03 ↔ renal dis., elderly	2.6±0.4 ↔ children	86± 8	1g (A: 875/C: 125) every 8 h os ; 1 g every 8 h <i>i.v.</i>
Clavulante	75±21	1.3 <sup>d</sup>	2.8 <sup>d</sup>	22	0.9±0.1 ↑ neonates, renal dis. ↔ children	0.21±0.05 ↔ renal dis., children	3.6±1.0 ↓ renal dis. ↔ children	43±14	2g (16:1, A: 2000/C:125 mg, twice daily os 2.2 g every 8 h <i>i.v.</i> ..
Ampicillin	100 <sup>f</sup>	1	49.6	–	1.04	0.16	0.25	71	1.5g every 8 h <i>i.v.</i> o <i>i.m.</i>
Sulbactam			93.5		0.99 ↑ renal dis., children, neonates, cystic fib., elderly	0.10	0.17 ↑ renal dis., children, neonates, cystic fib.,elderly	71	
Piperacillin	–	–	264.4–277	21	↓post-partum 0.75–0.91	15	14.5	50–60	4.5g (P: 4/ T: 0.5)

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Urinary clearance (%)	Dose
Tazobactam	–	–	29.1–34 ↑renal dis., children	20–23	0.78–0.8 ↑renal dis.,children	18 ←→liver dis.	12.1 ←→liver dis. ↓neonates	50–60 ←→liver dis.	every 8 h <i>i.v.</i>

↑: INCREASE; ↓: REDUCTION; ←→: NO CHANGE. **a:** dose-dependent; dose: 375mg; reduction of about 50% at 3000mg; **b:** no change in absence of renal insufficiency; **c:** single dose 500mg *i.v.* in healthy elderly or single oral dose 500mg in adults; **d:** mean values after an oral dose 125mg (healthy adults). **e:** values after a dose of 500mg-500mg ampicillina-sulbactam; **f:** *i.m.*; **g:** mean values after single or multiple doses 4/0.5g piperacillin/tazobactam.

TABLE 42 Main pharmacokinetics parameters of carbapenems and suggested dosing. Reproduced from [276, 277] with permission from publisher.

Antibiotic	T <sub>max</sub> (h)	C <sub>max</sub> (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	V <sub>d</sub> (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Imipenem	<i>i.m.</i> : 1–2 <sup>b</sup>	<i>i.v.</i> : 60–70 <sup>b</sup> <i>i.m.</i> : 8.2–12 <sup>b</sup>	<20	0.9±0.1 ↑ neonates, nefrop., prem.  ←→cystic fib, children, elderly	0.23±0.05 ↑ neonates, prem., children  ←→cystic fib, nefrop., elderly	2.9±0.3 ↑ children ↓ nefrop.  ←→cystic fib, neonates, prem., burns, infiammazioni, elderly	69±15 ↓ neonates, infiammazioni  ←→cystic fib, children	500mg - 1g every 8 h <i>i.m./i.v.</i>
Cilastatin	–	–	~35	0.8±0.1 ←→neonates, prem.  ↑cystic fib, elderly	0.2±0.03 ↑ neonates, nefrop., prem.  ←→cystic fib, children, elderly	3.0±0.3 ↑ children ↓ nefrop., neonates, prem.  ←→cystic fib, elderly	70±3 ↓ neonates  ←→cystic fib,	
Meropenem	–	54.8–61.6 <sup>c</sup> 21.1–35.6 <sup>d</sup>	10–20	1–1.4 <sup>c</sup> 0.8–1.54 <sup>d</sup> ↑ children, elderly,	0.18–0.3 <sup>c</sup> 0.12–0.37 <sup>d</sup> ↑ children, surgery.	2.7–4 <sup>c</sup> 2.67–4.7 <sup>d</sup> ↓ children, elderly	65.8±8.8 <sup>c</sup> 83±4 <sup>d</sup> ↓ children, elderly	1g every 8 h <i>i.v.</i>

Antibiotic	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
				renal dis. ↓ cystic fib	↓ cystic fib	↑renal dis., cystic fib	↑renal dis., cystic fib	

↑: increase; ↓: reduction; ↔: no change; **a**: preparation ratio 1:1 (mg·mg<sup>-1</sup>); **b**: single dose of 1g *i.v.* (infusion time 30 min) or 750 mg *i.m.*; **c**: single dose 1 g; **d**: single dose 0.5 g.

TABLE 43 Main pharmacokinetics parameters of oral cephalosporins and suggested dosing. Reproduced from [278–282] with permission from publisher.

Antibiotic	Biodisposability (%)	T <sub>max</sub> (h)	C <sub>max</sub> (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	V <sub>d</sub> (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Renal clearance (%)	Dose
Cefaclor (II generation)	90	1 <sup>a</sup> 3.8 <sup>b</sup>	15 <sup>a</sup> 11 <sup>b</sup>	25	1 <sup>a</sup> 0.77 <sup>b</sup>	5.86 <sup>c</sup>	4.8–6.4 <sup>a</sup>	74.3±3.7 <sup>a</sup> 71.2±5.8 <sup>b</sup>	750mg every 12 h M.R.
Cefuroxime axetil (II generation)	32 (21–44) <sup>b</sup> ↑cibo	2–3 <sup>c</sup>	7–10 <sup>c</sup>	33±6	1.7±0.6 ↑ renal dis.  ←→children	0.20±0.04 ←→renal dis., elderly	Cl = 0.94Cl <sub>cr</sub> +0.28	96±10	500mg every 8–12 h
Cefixime (III generation)	47±15	3–4 <sup>e</sup>	1.7–2.9 <sup>e</sup>	67±1	3.0±0.4 ↑ renal dis.	0.30±0.03	1.3±0.2 ↓renal dis.	41±7	200–400mg every 12–24 h
Cefpodoxime proxetil (III generation)	50	2.8	2.6	<40	2.7 ↑ renal dis.	0.7± 0.07	3.4±0.6 ↓renal dis.	46	200mg every 12 h
Ceftibuten (III generation)	80	2	15	60–70	2.5	0.21–0.24	0.7–1.1	70	400mg every 12–24 h

↑; increase; ↓: reduction; ←→: no change. **a**: after 500 mg, IR (immediate release); **b**: after 750 mg, MR (modified release); **c**: cefuroxime axetil, prodrug; **d**: mean values after single oral dose 500 mg healthy volunteers; **e**: mean values after single oral dose 200 mg (capsule) healthy volunteers; **f**: prodrug, dose: 200 mg.

TABLE 44 Main pharmacokinetics parameters of parenteral cephalosporins and suggested dosing. Reproduced from [283–286] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Urinary clearance (%)	Dose
Cefazoline	>90	<i>i.m.</i> : 1.7±0.7 <sup>a</sup>	<i>i.v.</i> : 237±285 <sup>a</sup> <i>i.m.</i> : 42±9.5 <sup>a</sup>	89±2 ↓renal dis., cirrhosis, bypass cardiopolm, neonates, children	2.2±0.02 ↑renal dis., bypass cardiopolm, neonates ↓pregnancy, children	0.19±0.06 ↑renal dis., neonates ←→obesity, children, pregnancy, cirr.	0.95±0.17 ↓renal dis., bypass cardiopolm ↑ pregnancy ←→obesity, children, neonates, cirr.	80±16	1-2g every 8 h <i>i.v.</i> o <i>i.m.</i>
Cefotetan	–	<i>i.m.</i> : 1.5-3 <sup>b</sup>	<i>i.v.</i> , B: 336-491 <sup>b</sup> <i>i.v.</i> , I: 38 <sup>b</sup> <i>i.m.</i> : 91 <sup>b</sup>	85±4	3.6±1.0 ↑renal dis.	0.14±0.03 ←→renal dis.	Cl=0.23Clcr±0.14 ↓renal dis.	67±11	1-2g every 12 h <i>i.v.</i> o <i>i.m.</i>
Cefotaxime	–	<i>i.m.</i> : 0.5 <sup>d</sup>	<i>i.v.</i> : ~150 <sup>d</sup> <i>i.m.</i> : 20.5 <sup>d</sup>	36±3 ←→ cirrhosis <sup>e</sup>	1.1±0.3 ↑renal dis., cirrhosis <sup>e</sup> ←→obesity	0.23±0.06 ←→renal dis., obesity ↑ cirrhosis <sup>e</sup>	3.7±0.6 ↓renal dis., cirrhosis <sup>e</sup> , women ←→obesity	55±10	1-2g every 8-12 h <i>i.v.</i> o <i>i.m.</i>
Ceftazidime	<i>i.m.</i> : 91	<i>i.m.</i> : 0.7±1.3 <sup>f</sup>	<i>i.v.</i> : 119-146 <sup>f</sup> <i>i.m.</i> : 29-39 <sup>f</sup>	21±6	1.6±0.1 ↑renal dis., prem.,	0.23±0.02 ←→renal dis., cystic fib	Cl=1.05Clcr+0.12 ←→ cystic fib	84±4 ←→ cystic fib	2g every 8 h

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Urinary clearance (%)	Dose
Ceftriaxone	–	<i>i.m.</i> : 2-2.4 <sup>g</sup>	<i>i.v.</i> : 168 <sup>g</sup> <i>i.m.</i> : 114 <sup>g</sup>	90-95 <sup>h</sup> ↓ cirrhosis, children neon. ←→elderly	neon.,elderly ←→cystic fib 7.3±1.6 <sup>h</sup> ↑ renal dis. <sup>i</sup> ,bypass cardiopolm., elderly ←→ cirrhosis	↑elderly 0.16±0.03 <sup>h</sup> ↑bypass cardio-polm.,neon, cirrhosis.,cystic fib ←→ renal dis., elderly	0.24±0.06 <sup>h</sup> ↓renal dis.,elderly <sup>l</sup> neon. <sup>l</sup> ↑ cirrhosis.,cystic fib ←→bypass cardio-polm.	49±13 <sup>m</sup> ↑neon.,ba mb.	<i>i.v. o i.m.</i> 1-2g/die OD <i>i.v. o i.m.</i>
Cefepime	–	–	65±7 <sup>n</sup>	16-19	2.1 (1.3-2.4) <sup>o</sup> ↑ renal dist <sup>p</sup>	0.26 (0.24-0.31) <sup>q</sup>	1.8 (1.7-2.5) <sup>o</sup> ↓ renal dis <sup>p</sup>	80	2g every 12 h <i>i.v.</i>

**↑**: increase; **↓**: reduction; **←→**: no change. **a**: after a single dose 1g *i.v. o i.m.* healthy adults; **b**: Cmax mean values, from different studies, single dose 2g (*i.v.*), or mean Cmax and Tmax single dose 2 g *i.m.* healthy volunteers. **c**: active metabolite, desacetilcefotaxime, responds of around 16±4% of eliminated amount; T<sub>1/2</sub>=2,2±0,3 h after single dose *i.v.* 1 g; **d**: mean values Cmax after single dose *i.v.* (infusion time 25 min) 30 mg·kg<sup>-1</sup>, or single dose 1 g *i.m.* healthy adults. **e**: patients with liver cirrhosis or severe renal failure; **f**: mean values from studies on healthy volunteers: single dose 1g *i.v.* or *i.m.* **g**: mean values single dose 1g *i.v.* (infusion time 30 min) or *i.m.* bid at “steady-state” in adults; **h**: single dose; **i**: clearance can increase till 50 h in anephric patients with reduced non –renal clearance; **l**: reduced clearance of free drug; **m**: hepatic clearance; **n**: after single dose 1g *i.v.*; **o**: mean values Cl and T<sub>1/2</sub> from 16 studies (single dose); **p**: moderate-severe renal failure; **q**: mean values Vss from 6 studies (single dose).

TABLE 45 Main pharmacokinetics parameters of fluoroquinolones e suggested dosing. Reproduced from [287–289] with permission from author.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Ciprofloxain	60±12	0.6±0.2 <sup>a</sup>	os:2.5±1.1 <sup>a</sup> i.v.: 6.7 <sup>b</sup>	40	os: 3.3±0.4 i.v.: 4.2 <sup>b</sup> ↑ renal dis. ←→elderly	2,2±0.4 ↓ elderly ←→ cystic fibr	7.6±0.8 ↓ renal dis., elderly ↑ cystic fibr	50 ± 5	500-750mg every 12h os  400mg every 8-12h i.v.
Levofloxacin	99±10	1.6±0.8 <sup>c</sup>	os: 4.5±0.9 <sup>c</sup> i.v.:5.7±0.8 <sup>d</sup>	24-38	↓cistic.fibr os: 7±1 <sup>c</sup> i.v.: 6.7 ±0.7 <sup>d</sup> ↑ nefropat <sup>e</sup>	os :1.36±0.21 <sup>c</sup> i.v.:1.5±0.23 <sup>d</sup>	os:2.52 ±0.45 <sup>c</sup> i.v.:2.8±0.5 <sup>e</sup> ↓ renal dis. <sup>e</sup>	61-87	500mg every 12-24h os/i.v. or 750 mg iv oc 400mg/die os/i.v.
Moxifloxacin	86±1	2.0 (0.5–6.0) <sup>f</sup>	2.5±1.3 <sup>f</sup>	39.4±2.4	15.4±1.2	2.05±1.15	2.27± 0.24	21.9 ±3.6	

↑: increase; ↓: reduction; ←→: no change; **a**: after oral dose 500 mg bid for 3 days or more in COPD patients; **b**: after *i.v.* dose 400 mg; **c**: after single oral dose 500 mg. No significant accumulation with OD dosing; **d**: after single *i.v.* dose 500 mg; **e**: reduced Cl/F, severe renal failure; **f**: after single oral dose 400 mg.

TABLE 46 Main pharmacokinetics parameters of macrolides and ketolides, and suggested dosing. Reproduced from [290–293] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Azithromycin	34±19 ↑ Food (capsul)	2–3 <sup>a</sup>	0.4 <sup>a</sup>	7–50 <sup>b</sup>	40 ←→cirrhosis	31	9	12	500mg/die X 3 days os
Clarithromycin	↓ Food (suspension) 55±8 <sup>c</sup>	C: 2.8 <sup>d</sup> HC: 3 <sup>d</sup>	C: 2.4 <sup>d</sup> HC: 0.7 <sup>d</sup>	42–50	3.3±0.5 <sup>c</sup> ↑elderly, renal dis.,cirrhosis.	2.6±0.5 ←→elderly ↑ cirrhosis	7.3±1.9 <sup>c</sup> ↓ elderly, renal dis. ←→cirrhosis	36±7 <sup>c</sup> ←→elderly	500mg every 12 h os ed <i>i.v.</i>
Erythromycin	35±25 <sup>e</sup> ↓pregnancy <sup>f</sup>	B: 2.1–3.9 <sup>g</sup> S: 2–3 <sup>g</sup>	B: 0.9–3.5 <sup>g</sup> S: 0.5–1.4 <sup>g</sup>	84±3 <sup>g</sup> ←→ renal dis.	1.6±0.7 ↑ cirrhosis ←→ renal dis.	0.78±0.44 ↑ renal dis.	9.1±4.1 <sup>h</sup> ←→ renal dis.	12 ±7	500mg–1g every 6 h os
Telithromicin	57	1–2	1.8–2.27	60–70	9.81	–	2.98	13	800mg/die os

↑: increase; ↓: reduction; ←→: no change; **a**: after single oral dose 250mg/die adult patients with infections; **b**: dose-dependent binding; binding 50% at 0,05 mg·l<sup>-1</sup> and 12% at 0,5mg·l<sup>-1</sup> ; **c**: after oral dose 250mg. At higher doses, saturation of metabolic clearance determines the increase of % of renal clearance and half-life, and the decrease of Cl; **d**: mean values for clarithromycina (C) and 14-OH-clarithromycin (HC), after oral dose 500mg bid in healthy adults; **e**: erythromycin base; **f**: reduction of concentrations due to decrease of biodisposability (or

clearance increase); **g**: mean values range from studies with multiple doses 250mg of erythromycin base (B) or stearate-erythromycin (S); **h**: erythromycin is a substrate for CYP3A; N-demethylation. It is also carried by P-glicoprotein; **i**: single oral dose 800 mg.

TABLE 47 Main pharmacokinetics parameters of glycopeptides and suggested dosing. Reproduced from [294, 295] with permission from publisher.

Antibiotic	C <sub>max</sub> (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	V <sub>d</sub> (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Vancomycin	18.5 (15–25) <sup>a</sup>	30±11 ←→ nefrop.	5.6±1.8 ↑renal dis.,elderly ↓obesity	0.39±0.06 ↓obesity ←→renal dis., COPD.	Cl= 0.79Cl <sub>cr</sub> +0.22 ↓ renal dis.,elderly, neonates ←→obesity, COPD	79±11	7.5–15mg·kg <sup>-1</sup> every 6–12h <i>i.v.</i> or continuous infusion
Teicoplanin	43.2 <sup>b</sup> 12.3 <sup>c</sup>	>90	155–168 <sup>d</sup> 182 <sup>e</sup> ↑renal dis.	0.8–1.6 <sup>f</sup>	↑burns 10–13 <sup>g</sup> 8–12 (Cl renale) ↓ renal dis. ↑bacterial endocarditis	9	6mg·kg <sup>-1</sup> every 12h X 3 times and then every 24h <i>i.v.</i> or <i>i.m.</i>  12mg·kg <sup>-1</sup> every 12h X3 times and then every 24h <i>i.v.</i> or <i>i.m.</i> in patients with <i>S.aureus</i> endocarditis , septic arthritis or burns

↑: increase; ↓: reduction; ↔: no change; **a**: after single dose 1g *i.v.* (infusion time 1h) bid, or 7,5mg·kg<sup>-1</sup> *i.v.* (infusion time 1h) qid, adult patients with staphylococcus and streptococcus infections. Levels of 37–152 mg·l<sup>-1</sup> are associated to ototoxicity; **b**: 6mg·kg<sup>-1</sup> *i.v.*, single dose, after 0.5 h; **c**: 6mg·kg<sup>-1</sup> *i.m.*, single dose, after 4 h; **d**: *i.v.*; **e**: *i.m.*; **f**: 6–15 mg·kg<sup>-1</sup> *i.v.*, single dose; **g**: 3–30 mg·kg<sup>-1</sup>, *i.v.*, single dose.

TABLE 48. Main pharmacokinetics parameters of aminoglycosides and suggested dosing. Reproduced from [296–298] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Renal clearance (%)	Dose
Amikacin	–	–	26±4 <sup>a</sup>	4±8 <sup>b</sup>	2.3±0.4 ↑ renal dis.  ←→ obesity  ↓ burns, cystic fibr, children	0.27±0.06 ←→ elderly, children, cystic fib  ↓ obesity  ↑ neonates	1.3±0.6 Cl=0.6Clcr+0.14 ↓ obesity  ↑ cystic fib	98	15mg·kg <sup>-1</sup> ·die <sup>-1</sup> <i>i.m./i.v.</i> OD
Gentamicin	<i>i.m.</i> : ~100	<i>i.v.</i> : 1 <sup>c</sup> <i>i.m.</i> : 0.3–0.75 <sup>c</sup>	<i>i.v.</i> : 4.9±0.5 <sup>c</sup> <i>i.m.</i> : 5.0±0.4 <sup>c</sup>	<10	2–3 <sup>d</sup>	0.31±0.10 ←→renal dis., elderly, cystic fib, children  ↓ obesity  ↑ neonates	Cl= 0.82Clcr+0.11 ↓ obesity	>90	5mg·kg <sup>-1</sup> ·die <sup>-1</sup> <i>i.m./i.v.</i> OD

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Renal clearance (%)	Dose
Tobramicin	inhalation: 9±8	<i>i.m.</i> : 0.3–0.75 <sup>c</sup>	<i>i.v.</i> : 4.6±0.5 <sup>c</sup> <i>i.m.</i> : 5.2±0.6 <sup>c</sup>	<10	2.2±0.1 <sup>e</sup> ↑renal dis., neonates,prem. ←→obesity, cystic fib ↓burns	0.33±0.04 <sup>f</sup> ↓ obesity ←→ renal dis., burns, elderly ↑ cystic fib, neonates	Cl= 0.98Cl <sub>cr</sub> ±32% <sub>g</sub> ↓ obesity ↑ cystic fib	90	5mg·kg <sup>-1</sup> ·die <sup>-1</sup> <i>i.m./i.v.</i> OD

↑: increase; ↓: reduction; ←→: no change. **a**: after single dose (infusion time 1 h 6.3±1.4 mg·kg<sup>-1</sup>), tid at “steady-state” in patient with normal renal function; **b**: at a serum concentration of 15 mg·l<sup>-1</sup>; **c**: after *i.v.* dose 100 mg (infusion time 1h) or 100 mg *i.m.*, healthy adults; **d**: gentamicin has a long T<sub>1/2</sub> (53±25 h) that justifies a prolonged renal excretion; **e**: tobramycin has a long T<sub>1/2</sub> (146±75 h), it reflects a slow release from tissues and justifies a prolonged renal excretion; **f**: central compartment volume; **g**: Cl<sub>cr</sub> ml·min<sup>-1</sup>·kg.

TABLE 49 Main pharmacokinetics parameters of tetracyclines and suggested dosing. Reproduced from [299, 300] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Doxycyclin	93	os: 1–2 <sup>a</sup>	<i>i.v.</i> : 2.8 os: 1.7–2	88±5 ↓renal dis. (71±3)	16±6 ←→ renal dis., elderly, Hyperlipoprot.	0.75±0.32 ↓ elderly, Hyperlipoprot.	0.53±0.18 ↓ elderly, Hyperlipoprot. ←→ renal dis.	41±19	200mg·die <sup>-1</sup> os o <i>i.v.</i>
Minocyclin	95–100	os: 2–4 <sup>b</sup>	<i>i.v.</i> : 3.5 <sup>b</sup> os: 2.3–3.5 <sup>b</sup>	76	16±2 ←→cirrosi, Hyperlipoprot., renal dis. <sup>c</sup>	1.3±0.2 ↓ Hyperlipoprot.	1.0±0.3 ↓ Hyperlipoprot.	11±2	100mg every 12h os
Tetracyclin	77	os: 4	<i>i.v.</i> : 16.4±1.2 <sup>d</sup> os: 2.3±0.2 <sup>d</sup>	65±3	10.6±1.5	1.5±0.1	1.67±0.24	58±8	250–500mg every 6h os  0.5–1g every 12h <i>i.v.</i>

↑: increase; ↓: reduction; ←→: no change. **a**: after single oral dose 100mg; **b**: mean values after single dose *i.v.* (infusion time 1 h) 200mg or 100mg bid at “steady-state”; **c**: increase of T<sub>1/2</sub> in patients with reduced clearance. With a Cl of 18–45ml·min<sup>-1</sup> no accumulation has been recorded after multiple doses, in healthy subjects; **d**: after single dose *i.v.* 10 mg·kg<sup>-1</sup> or oral 250 mg (empty stomach with water).

TABLE 50 Main pharmacokinetics parameters of other antibiotics and suggested dosing. Reproduced from [301–308] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Clindamycin	~87 <sup>a</sup> topica: 2	–	<i>i.v.</i> : 17.2±3.5 <sup>b</sup> <i>os</i> : 2.5 <sup>c</sup>	93.6±0.2	2.9±0.7 ↑ prem.  ←→ children, renal dis., pregnancy	1.1±0.3 <sup>d</sup> ←→ renal dis., children	4.7±1.3 ←→ children	13	600–900mg every 8 h <i>os</i> <i>i.v.</i> o <i>i.m.</i>
Linezolid	100	1.3 <sup>e</sup> 1.0 <sup>f</sup> 0.5 <sup>g,h</sup>	12.7 <sup>e</sup> 21.2 <sup>f</sup> 12.9 <sup>g</sup> 15.1 <sup>h</sup> ↑ donne	31	5.5 <sup>e</sup> 4.5 <sup>g</sup> ↑ liver dis.  ↓ children	40–50	100–200 ↓ liver dis.  ↑ hemodial., children	30	600mg every 12 h <i>os</i> o <i>i.v.</i>
<sup>i</sup> Metronidazol	99±8 <sup>l</sup> ←→pat.cronic.	<i>os</i> : 2.8 <sup>m</sup> VA: 11±2 <sup>m</sup>	<i>i.v.</i> : 27(11– 41) <sup>m</sup> <i>os</i> : 19.8 <sup>m</sup> VA: 1.9±0.2 <sup>m</sup>	11±3	8.5±2.9 ↑ neonates,cirr.  ←→ nefrop., pregnancy, Chron., children	0.74±0.10 ←→ nefrop., cirr., malattia Chron	1.3±0.3 ↓ cirr., neon.  ←→ nefrop., pregnancy, Chronn.,elderly	10±2	7.4 mg·kg <sup>-1</sup> (~500 mg) every 6 h <i>i.v.</i>  500mg every 6 h <i>os</i>
Rifampin	– <sup>o</sup>	1–3 <sup>p</sup>	6.5±3.5 <sup>p</sup>	60–90	3.5±0.8 <sup>q</sup> ↑ hepatitis, cirr. renal dis. <sup>r</sup>  ←→ children,	0.97±0.36 ↑ neonates  ←→ elderly	3.5±1.6 <sup>q</sup> ↑ neonates  ←→ elderly <sup>r</sup>	7±3 ↑ neonates	450–600mg every 12 h <i>os</i> (10 mg·Kg <sup>-1</sup> )

					elderly		↓ renal dis.		
Quinupristin	–	–	2.3±0.5 <sup>s</sup>	23–32	0.97±0.20	0.79±0.40	17.2±3.43	15.1	7.5mg·kg <sup>-1</sup> every 8 h <i>i.v.</i>
							↓liver dis. <sup>u</sup> ,renal dis. <sup>t</sup>		
Dalfopristin	–	–	6.4±2.7 <sup>s</sup>	50–56	0.52±0.21	0.43±0.29	19.8±10.7	18.7	
							↓ liver dis. <sup>u</sup> ,renal dis. <sup>t</sup>		

↑: increase; ↓: reduction; ↔: no change; **a**: clindamicin cloridrate per os; **b**: single dose *i.v.* (infusion time 30 min) 1200mg clindamicin phosphate (prodrug), bid at steady-state in healthy adults male; **c**: after single oral dose 150mg clindamicin hydrochlorite in adults; **d**: V<sub>area</sub>; **e**: single oral dose 600mg; **f**: 600mg every 12 h oral; **g**: dose singola di 600mg, *i.v.* **h**: 600mg every 12 h *i.v.* **i**: active metabolite with renal accumulation; **l**: bioavailability range 67–82% rectal use; **m**: after 500mg *i.v.* (infusion 20 min) t.i.d or oral dose 500 mg t.i.d; **n**: active metabolite; **o**: insufficient data; **p**: after 600mg od for 15–18 days in TB patients; **q**: T<sub>1/2</sub> longer at high doses; **r**: not observed at 300mg; **s**: single dose 10mg·kg<sup>-1</sup> *i.v.* (1 h infusion); **t**: severe renal complication; **u**: mild-moderate liver complications.

TABLE 51 Pharmacodynamics and pharmacokinetics of chemotherapeutic antimicrobials: evidence table

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
AMBROSE [259]	To determine relationship between fluoroquinolone exposure and clinical and microbiological efficacy.	CCS	3a+
CRAIG [260]	To study post-antibiotic effect in animal infection models	NON-SYSTEMATIC	6a-
CRAIG [261]	To study cephalosporin pharmacodynamics in animal infection models	NON-SYSTEMATIC	6a-
CRAIG [262]	To describe pharmacodynamic activity of antimicrobials	NON-SYSTEMATIC	6a-
GOTFRIED [263]	To compare lining fluid, and alveolar macrophage concentrations of levofloxacin and ciprofloxacin	RCT	2a+
NIGHTINGALE [309]	To describe the effect of the area under the plasma concentration-time curve relative to the minimum inhibitory concentration on bacteria	NON-SYSTEMATIC	6a-
SCHENTAG [310]	To describe what have we learned from pharmacokinetic and pharmacodynamic theories	NON-SYSTEMATIC	6a-
MOORE [311]	To study the importance of the ratio of peak concentration to minimal inhibitory concentration in aminoglycoside therapy	CCS	3a+
HYATT [312]	To describe determinants of outcome in antimicrobial therapy	NON-SYSTEMATIC	6a-
MACGOWAN [313]	To review the pharmacodynamic properties of penicillins, cephalosporins, carbapenems, quinolones, glycopeptides and aminoglycosides	NON-SYSTEMATIC	6a-
WILDFEUER [270]	To document the concentrations of ampicillin and sulbactam in serum and in various compartments of the respiratory tract	CCS	3a-
OLSEN [314]	To describe the intrapulmonary	CCS	3a-

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
MAZZEI [315]	pharmacokinetics of oral azithromycin To document the concentrations of cefaclor in suction blister fluid (SBF) and alveolar epithelial lining fluid (ELF).	CCS	3a-
BENONI [316]	To document the pharmacokinetics of ceftriaxone in pleural fluid	CCS	3a-
DECRE [317]	To review the pharmacokinetics of fluoroquinolones	NON SYSTEMATIC	6a-
PATEL [318]	To study the bronchopulmonary and plasma pharmacokinetics of clarithromycin and azithromycin	CCS	3a+
CONTE [319]	To study the intrapulmonary pharmacokinetics of clarithromycin and erythromycin	CCS	3a+
BENONI [320]	To study the pharmacokinetics of Imipenem	CCS	3a-
LEE [321]	To evaluate the pulmonary tissue distribution of levofloxacin,	CCS	3a-
CONTE [322]	To determine the steady-state intrapulmonary concentrations and pharmacokinetic parameters of orally administered linezolid	CCS	3a-
BERGOGNE-BEREZIN [323]	To evaluate the ability of meropenem to reach the bronchial lumen.		3a-
SIMON [324]	To construct a population pharmacokinetic model for moxifloxacin disposition in plasma and bronchial secretions in patients with severe bronchopneumonia who were mechanically ventilated.	CCS	3a-
TOMASELLI [325]	to measure piperacillin and tazobactam penetration into the extracellular space fluid of pneumonic human lung	CCS	3a-
MULLER-SERIEYS	To study the penetration of	CCS	3a-

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
[326]	telithromycin into bronchopulmonary tissues		
MAZZEI [327]	To study the pharmacokinetics of tobramycin, including the penetration into suction blister fluid.	CCS	3a-
CRUCIANI [328]	To study Vancomycin penetration into lung tissue	CCS	3a-
SUM [271]	To study serum kinetics and urinary excretion of lenampicillin, bacampicillin and amoxycillin.	RCT	2a+
FERSLEW [272]	To study the pharmacokinetics and urinary excretion of clavulanic acid	CCS	3a-
PETITPRETZ [273]	To compare a pharmacokinetically enhanced formulation of oral amoxicillin-clavulanate to amoxicillin-clavulanate 1000/125 , in community- acquired pneumonia	RCT	2a+
MOLINARO [274]	To study the bioavailability of two different oral formulations of amoxicillin	RCT	2a-
NATHWANI [275]	Systematic review of penicillin pharmacology	MA	1a+
SIGNS [276]	To study the pharmacokinetics of imipenem	CCS	3a-
DRUSANO [277]	To produce a review of the pharmacokinetics of meropenem	NON SYSTEMATIC	6a-
SATTERWHITE [278]	To study the pharmacokinetics and bioavailability of cefaclor advanced formulation	CCS	3a-
DONN [279]	To determine the bioequivalence of two cefuroxime axetil formulations.	RCT	2a+
KEES [280]	To compare the relative bioavailability of three formulations of cefixime	CCS	3b-
BORIN [281]	To compare the bioavailability of cefpodoxime proxetil tablets relative to an oral solution of cefpodoxime proxetil	RCT	2b-
LIN [282]	To comparative the	CCS	3b-

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
	bioavailability of ceftibuten, in capsule and suspension dosage forms.		
ZIMMERMAN [283]	To study the pharmacokinetic parameters of Cefotetan	CCS	3a-
BORNER [284]	To study the pharmacokinetics of ceftriaxone after subcutaneous and intravenous administration	CCS	3a-
DELSIGNORE [285]	To determine the disposition and bioavailability of ceftriaxone	CCS	3a-
BARBHAIYA [286]	To study the steady state pharmacokinetics, absolute bioavailability, and dose proportionality of cefepime	CCS	3a-
BEGG [287]	To study the pharmacokinetics of ciprofloxacin and fleroxacin in plasma and sputum of patients with an acute exacerbation of chronic bronchitis or bronchiectasis	RCT	2b-
CHIEN [288]	To compare the pharmacokinetics of once-daily oral levofloxacin or intravenous levofloxacin	RCT	2a+
STASS [289]	To study the pharmacokinetics of moxifloxacin and its metabolites M1 (sulpho-compound) and M2 (acyl-glucuronide)	RCT	2b-
FOULDS [290]	To study the effect of food on bioavailabilities of three new formulations of azithromycin	CCS	3a-
CHU [291]	To determine the absolute bioavailability of clarithromycin	RCT	2b-
RUTLAND [292]	To study the effect of food on the bioavailability of two formulations of erythromycin.	RCT	2b-
PERRET [293]	To determine the pharmacokinetics and absolute oral bioavailability of telithromycin in young and elderly healthy subjects.	RCT	2b-
VERBIST [294]	To determine the <i>in vitro</i> activity of teicoplanin, against 456 gram-positive cocci.	CCS	3b-

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
LEADER [295]	To perform a review of pharmacokinetics of vancomycin	NON-SYSTEMATIC	6a-
BAUER [296]	To determine aminoglycoside pharmacokinetics in normal weight and morbidly obese patients	CCS	3a+
REGAMEY [297]	To compare pharmacokinetics of tobramycin and gentamicin	CCS	3a-
AARONS [298]	To determine population pharmacokinetic parameters of tobramycin	PCS	3a+
SAIVIN [299]	To provide a review of clinical pharmacokinetics of doxycycline and minocycline	REVIEW (NON SYSTEMATIC)	6a-
GARTY [300]	To study the effect of cimetidine and antacids on gastrointestinal absorption of tetracycline	RCT	2b-
MAZUR [301]	To investigate the pharmacokinetics and relative bioavailability of clindamycin	CCS	3b-
GATTI [302]	To study the absolute oral bioavailability and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS	CCS	3b-
MEAGHER [303]	to develop a population model of the pharmacokinetics of intravenous and oral linezolid.	PCS	3b+
PATON [304]	To compare bioavailability of two tablet preparations of metronidazole	RCT	2b+
LAU [305]	To evaluate the pharmacokinetics of metronidazole at different dosage levels in normal subjects.	CCS	3b+
PANCHAGNULA [306]	To study the bioequivalence of the antituberculous drug rifampicin in a four-drug combination (rifampicin, isoniazid, pyrazinamide and ethambutol) and separate formulations of the drugs at the same dose levels	CCS	3b+
LOOS [307]	To study the pharmacokinetics	CCS	3b+

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
CHEVALIER [308]	of rifampicin and its major metabolites, 25-desacetyl rifampicin and 3-formylrifampicin, To study the pharmacokinetics and safety of two regimens of quinupristin/dalfopristin	CCS	3b-

MA: meta-analysis (or systematic review); RCT: randomised controlled trial; PCS: prospective cohort study; RCS: retrospective cohort study; CCS: case control study.

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