Diploma Thesis

Incidence and Etiology of Bacteremia in Patients with Community-Acquired Pneumonia (CAP)

submitted by

Christian Windhagauer

for the academic degree of

Doktor der gesamten Heilkunde

(Dr. med. univ.)

at the

Medical University of Graz

conducted at the

Division of Infectious Diseases

Department of Internal Medicine Graz

under the guidance of

Univ.-Prof. Dr.med.univ. Robert Krause

Assoz. Prof. Priv.-Doz. Dr.med.univ. Ines Zollner-Schwetz

Graz, 05.08.2021

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 05.08.2021 Christian Windhagauer eh.

Acknowledgements

At the beginning I would like to thank Univ.-Prof. Dr.med.univ. Robert Krause and Assoz. Prof. Priv.-Doz. Dr.med.univ. Ines Zollner-Schwetz for providing the topic as well as the complication-free handling and the support.

A big thank you goes to my parents, Gabi and Franz, who always believe in me, support me in every situation with all their energy and give me secure backing.

I would also like to thank my sister, Eva-Maria, who has an open ear for me anytime, offers me advice in numerous situations and on whom I can always rely.

Last but not least, I would like to thank my friends Patrick and the “Moises” Jan, Marco, Mario, Markus and Timon, who are an enrichment for my life and made the time during my studies unforgettable.

For Grandma Gerti

Table of Contents

Abbreviations and Their Explanation

CAP	Community-acquired pneumonia
NHAP	Nursing home-acquired pneumonia
HCAP	Healthcare-associated pneumonia
HAP	Hospital-acquired pneumonia
AP	Aspiration pneumonia
BC	Blood culture(s)
FP	Family practice
PSI	Pneumonia severity index
ICU	Intensive care unit
CXR	Chest X-ray

List of Figures

List of Tables

Zusammenfassung

Hintergrund: Die ambulant erworbene Pneumonie ist nach wie vor eine der wichtigsten Krankheitsentitäten weltweit, welche schwere Verläufe annehmen und oft lebensbedrohlich werden kann. Sowohl die Inzidenz als auch die Ätiologie der Bakteriämie bei Patienten/Patientinnen mit einer ambulant erworbenen Pneumonie sind eigentlich nicht gut bekannt, bilden jedoch eine wichtige Grundlage für die Auswahl spezifischer Antibiotika.

Ziel: Ziel dieser Arbeit ist es, Inzidenz und Ätiologie der Bakteriämie bei Patienten/Patientinnen mit einer ambulant erworbenen Pneumonie in verschiedenen europäischen Ländern zusammenzufassen, um eine Antwort hinsichtlich der Behandlung äußern zu können. Ebenso wird auf die allgemeine Inzidenz der ambulant erworbenen Pneumonie in den verschiedenen europäischen Ländern eingegangen und es werden Vergleiche bezüglich Erregerspektrum zwischen Blutkulturen und Kulturen aus unterschiedlichen Materialien gezogen.

Methoden: Es wurden Fachbücher, aktuelle Leitlinien sowie Artikel aus elektronischen Datenbanken herangezogen. Für die Suche nach Studien und wissenschaftlichen Artikeln wurden die Datenbanken PubMed und Google Scholar verwendet.

Ergebnisse: Die Inzidenz der ambulant erworbenen Pneumonie hat in allen untersuchten europäischen Ländern in den letzten Jahren zugenommen. Ebenso konnte gezeigt werden, dass es einen Zusammenhang zwischen Alter und Inzidenz gibt. Die Inzidenz nahm mit dem Alter zu.

Hinsichtlich der Inzidenz der Bakteriämie waren in etwa 7-10% der Blutkulturen bei Patienten/Patientinnen mit ambulant erworbener Pneumonie positiv.

In Blutkulturen war der mit Abstand häufigste Erreger Streptococcus pneumoniae, gefolgt von Escherichia coli, Staphylococcus aureus und Haemophilus influenzae. Im Vergleich zu Blutkulturen (3-4%) fand sich in Kulturen aus unterschiedlichen Materialien (Sputum, Blut, tracheobronchiales Aspirat, bronchoskopische Lavage, etc.) der Erreger Hämophilus influenzae mit (5-15%) verhältnismäßig häufiger. Ebenso konnte das Bakterium Mycoplasma pneumoniae in isolierten Blutkulturen nicht nachgewiesen werden und wurde häufiger bei jüngeren Patienten/Patientinnen entdeckt. Die Erreger selbst waren in den untersuchten europäischen Ländern in Bezug auf ihre Häufigkeit recht ähnlich.

Die leitliniengerechte antimikrobielle Therapie umfasst die meisten Erreger aus den Blutkulturen. Dennoch ist die Identifizierung des verursachenden Erregers wichtig, um eine gezielte Therapieänderung oder -anpassung vorzunehmen.
Bezüglich der Nützlichkeit von Blutkulturen kann aufgrund einer geringen Anzahl an Studien keine eindeutige Aussage getroffen werden und es sind diesbezüglich weitere Untersuchungen notwendig.

Abstract

Background: Community-acquired pneumonia remains one of the most important disease entities worldwide, which can take severe courses and often become life-threatening. Both the incidence and etiology of bacteremia in patients with community-acquired pneumonia are actually not well known; yet, they form an important construct for the selection of specific antibiotics.

Aim: The aim of this work is to summarize the incidence and etiology of bacteremia in patients with community-acquired pneumonia in different European countries, in order to be able to express an answer regarding the treatment. Furthermore, the general incidence of community-acquired pneumonia in different European countries will be discussed and, concerning the pathogen spectrum, comparisons will be drawn between blood cultures and cultures from different types of samples.

Methods: Reference books, current guidelines, and articles from electronic databases were consulted. PubMed and Google Scholar databases were used to search for studies and scientific articles.

Results: The overall incidence of community-acquired pneumonia has increased in all European countries studied in recent years. Similarly, it was shown that there is a correlation between age and incidence. The incidence increased with age.

When it comes to the incidence of bacteremia, about 7-10% of blood cultures were positive. As for blood cultures, the most common pathogen by far was Streptococcus pneumoniae, followed by Escherichia coli, Staphylococcus aureus, and Haemophilus influenzae. Compared to blood cultures (3-4%), the pathogen Haemophilus influenzae was found more frequently (5-15%) in cultures from different types of samples (sputum, blood, tracheobronchial aspirate, bronchoscopic lavage, etc.). Similarly, the bacterium Mycoplasma pneumoniae could not be detected in isolated blood cultures and was more often detected in younger patients. The pathogens themselves were quite similar in terms of frequency in the European countries studied.

The guideline-based antimicrobial therapy includes the most pathogens from blood cultures. Nevertheless, identifying the causative pathogen is important in order to make a targeted change or adjustment in therapy.

As for the usefulness of blood cultures, no clear statement can be made due to the small number of studies and the fact that further investigation is needed in this regard.

1 Introduction

1.1 Definition of Pneumonia

“Pneumonia is defined pathologically and anatomically as inflammation of mainly the alveoli, the Interstitium and/or the supplying bronchi by pathogenic agents” (1).
Pneumonia develops by:

- the aerogenic path (droplet infection).
- inhalation of aerosols, containing exogenous pathogens.
- microaspiration of microbially contaminated respiratory secretions or, rarely, via hematogenous spread.

1.1.1 Types of Pneumonia

Three major types of pneumonia are distinguished, namely lobar pneumonia, lobular pneumonia and interstitial pneumonia. Each of them is briefly highlighted below.
If the inflammation spreads to several alveoli within one lobe, it is called lobar pneumonia, whereas bronchopneumonia affects alveoli of different segments (1). In contrast, in interstitial pneumonia, the main focus of inflammation is in the extra-alveolar tissues, yet alveolar structures may also be affected in this form (1).

Lobar Pneumonia
This model is divided into four phases (2).
1. Coupling
2. The red hepatization stage
3. The gray hepatization stage
4. The yellow hepatization stage

The most common pathogen causing lobar pneumonia is Streptococcus pneumoniae, but pathogens such as Klebsiella pneumoniae or Legionella pneumophila can also cause it (3).

Lobular Pneumonia

The most frequent form of lobular pneumonia is bronchopneumonia.

Pathogens that can trigger this form are mainly Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa and some fungi (3, 4).

Interstitial Pneumonia

This type can be divided into 3 forms (2)

1) The septal form
2) The peribronchiolar form
3) The fibrosing form

Classical pathogens are viruses, especially influenza viruses but also mycoplasma, pneumocystis, chlamydia or Coxiella burnetii. (1-4).

1.2 Definition and Classification of Community-Acquired Pneumonia

1.2.1 Pneumonia Triad

Pneumonia can be split up into 3 sections, referred to as the pneumonia triad (5). This classification is based on the mode of acquisition (community, which is outside the hospital; or during or after a hospital stay) and immune status of the host.

1) Community-acquired pneumonia (CAP)
   Place of Occurrence: outside the hospital; immune status: immunocompetent
2) Hospital-acquired pneumonia (HAP)
   Place of Occurrence: inside the hospital; immune status: immunocompetent
3) Pneumonia in the immunosuppressed host
   Place of Occurrence: outside or inside the hospital; immune status: severe immunosuppression

Table 1: Pneumonia Classification

The pneumonia triad with the most important aspects as well as the most frequent pathogens from Ott, Ambulant erworbene und nosokomiale Pneumonie (6).

Pneumonia form	Immune status of the host	Location	Most common pathogens
CAP	immunocompetent	Outside the hospital	- Pneumococcus - H. Influenzae - Mycoplasma
HAP	immunocompetent	Inside the hospital *	additionally MRE - S. aureus (incl. MRSA)
Pneumonia in the immunosuppressed host	immunosuppressed	Outside or inside the hospital	opportunistic pathogens - Pneumocystis jirovecii - Aspergillus and other molds - Viruses

* >48 hours or hospitalized in the past three months

CAP, which is acquired outside the hospital, is the main subject of the present work. In the following chapter, the two other groups, i.e. HAP and pneumonia in the immunosuppressed host, are described briefly and the criteria for assignment to each group are outlined.

Hospital-Acquired Pneumonia

The second major group of the aforementioned classification is HAP. This form is acquired in hospital and develops in previously healthy patients into oropharyngeal or tracheobronchial colonization, which has an impact on the expected pathogen spectrum (7). In many epidemiologic studies, pneumonia is classified as hospital-acquired if it develops >48 h after hospital admission or when patients have been hospitalized in the past three months. However, the spectrum of pathogens can still change up to 92 h after admission. The natural pathogen spectrum of the upper respiratory tract includes germs such as Streptococcus pneumoniae, Staphylococcus aureus and Haemophilus influenza; even so, nosocomial pathogens like multidrug-resistant Enterobacteria or Pseudomonas

aeruginosa may additionally occur up to 92 h thereafter. In individual cases, it is also possible to find opportunistic pathogens such as Aspergillus spp..
The incidence of HAP is decreasing in the past, which might be due the use of noninvasive ventilation, and besides, hygiene standards have improved significantly on an international level in recent years (7).

Pneumonia in the Immunosuppressed Host

In addition to the previously mentioned groups, community-acquired and hospital-acquired pneumonia, pneumonia in the immunosuppressed is the third pillar of the pneumonia triad. This type of pneumonia is characterized by different features. It affects patients with severe immunosuppression, which is associated to a relevant risk for opportunistic infections. These include pathogens such as Pneumocystis jirovecii, fungi, viruses (cytomegalovirus, herpes simplex, varicella/zoster virus), and atypical mycobacteria (2). The place of origin is of minor importance, whereas the type and severity of immunosuppression are much more decisive with regard to the expected spectrum of pathogens (8).

Table 2: Condition Severe Immunosuppression

Typical conditions with severe immunosuppression from Randerath W. Pneumonien. In: Herold G, editor. Innere Medizin (2).

Typical conditions with severe immunosuppression
Neutropenia <1000/µL
Therapy with immunosuppressants (e.g. cytostatics, systemic steroids, TNF α blocker)
Organ or Stem cell transplantation
Antibody Deficiency Syndrome
Congenital Immunodeficiencies
HIV or AIDS

1.2.2 Subgroups

1.2.2.1 Community-Acquired Pneumonia of the Elderly Patient

Interest in older people with pneumonia has increased due to rising life expectancy and population morbidity in developed countries. In this context, individuals aged 65 or more fell into the category “elderly”, while persons between 70 and 80 years of age were labeled “very elderly” (8). Complication rate, hospitalization, and prognosis, examined in the elderly, were significantly worse with this patient population. Thus, a correlation between deteriorating parameters with increasing age could be observed. As for the pathogen spectrum, with the exception of a lower incidence of Mycoplasma pneumoniae, no specific changes were noted (8-10).

1.2.2.2 Community-Acquired Pneumonia of the Younger Patient

Recently, attention has also been paid to younger patients, i.e <65 years of age. Comorbidities are significantly less common in younger patients, as is short-term mortality in this population, and the spectrum of pathogens, moreover, differs from CAP in the elderly (11).

Table 3: Subgroups

Differentiation of subtypes with respect to various factors from Ewig, Definition und Abgrenzungen. In: Ewig S, editor. Ambulant erworbene Pneumonie (8).

	Pneumonia of the younger patient (<65 years) Functionality good	**Pneumonia of the elderly patient (≥65 years) Functionality good**	**Pneumonia regardless of age Functionality poor**
Initial severity	Less heavy	Heavy	Heavy
Complications	Rare	more frequent	more frequent
Multi-resistant pathogens	Very rare	Very rare	Rare
Therapy target change: symptom control*	Rare	Rare, more common at very old age	frequent
Fatal outcome	Low (<5 %)	Increased (<10 %)	High (20-40 %)

* Therapy for palliative care

1.2.2.3 Nursing Home-Acquired Pneumonia

Looking more closely at the subgroups, NHAP has to be mentioned, which represents the largest part of the subgroups (12). This Subgroup was classified with suspected change in pathogen spectrum. When the pathogens of CAP and NHAP were compared, minor differences in the germ spectrum were observed (13). The pathogen Streptococcus pneumonia was most common in both groups. Staphylococcus aureus was confirmed more often in the NHAP group, whereas Haemophilus influenzae and Mycoplasma pneumoniae were less frequent. In people over 85 years of age, atypical pathogens were more common in both groups. Chlamydophila pneumoniae and Streptococcus pneumoniae were found more frequently in the NHAP group (14). Age, comorbidity, and resulting functionality were, in contrast to pathogens, the key prognostic criteria that determine the mortality of patients with pneumonia from nursing homes (13). Both short- and long-term mortality in patients older than 65 years was significantly higher in the NHAP group than in the CAP group (15).

1.2.2.4 Healthcare-Associated Pneumonia

This group is an extension of the NHAP group described above. The approach behind this is based on the assumption that all patients who are cared for or treated in healthcare settings have an increased risk of developing pneumonia with multidrug-resistant germs. However, this assumption was refuted on the basis of low-quality evidence (16). Similarly, the concept of HCAP led to overtreatment of patients (17). Based on these arguments, there is no need to divide HCAP, as a separate group, from CAP.

1.2.3 Special Forms of Pneumonia

1.2.3.1 Aspiration Pneumonia

AP is a special form of CAP. The definition of aspiration is characterized by oropharyngeal or gastric fluid entering the lower airway (18). AP is the pulmonary consequence of aspiration. The bacterial etiology of AP is considered to be complicated because there are always variables that limit the conduct of multiple studies, such as the number of participants or obtaining clean cultures. It is also difficult to draw conclusions about a specific pathogen, since AP is, in many cases, treated with antibiotics that cover a broad range of pathogens. AP is caused by: Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and gram-negative rods as well as anaerobes (19).

1.2.3.2 Travel Associated Pneumonia

Pneumonia acquired during long-distance travel is another special form of pneumonia (12). The majority of pathogens causing travel associated pneumonia is similar to that in Europe (20). Common pathogens include Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, influenza viruses, and Legionella pneumophila. Nonetheless, there may be individual pathogens and resistances in each country that should be taken into account. After all, not only bacteria can cause pneumonia, but also viruses, parasites or fungi (20).

For this reason, travelers showing typical symptoms of CAP should be asked certain questions to assess the possible spectrum of pathogens acquired during vacation in specific countries

- Which country or countries/places/regions were visited?
- What was the type of travel? (Solo or group travel and type of activity)
- How long did the trip last?
- Was there any contact with animals?
- What was the travel season?
- What protective measures were taken?
- Which foods were consumed?

Through examination of patient history might give a hint for rare specific etiologies like histoplasmosis, paracoccidioidomycosis, Paragonimus westermani etc.

1.2.3.3 Epidemic Pneumonia

The last special form consists of pneumonia caused by an epidemic or local outbreak (12). A good example of an epidemic/pandemic disease would be the Corona virus SARS COV 2 that emerged in Wuhan in 2019. Within a few weeks or months, the virus spread worldwide with devastating consequences. Intensive research has provided insight into the structure and genetic makeup of the corona virus, as well as its interactions with a characterized receptor, its host source, and epidemiological properties (21). This also made it possible to start developing a vaccination as early as possible.
Local outbreaks can also cause pneumonia, as shown in this study, where some people became infected at a farmers' market (22).

1.2.4 Classification of Community-Acquired Pneumonia

The CAP is divided into groups 1a, 1b, and 2, according to the guidelines for CAP of 2016. (12). The groups determine the necessity of hospitalization, extent of diagnostic procedures and treatment. The assignment to a group is based on the criteria of functionality as well as the severity of CAP. Patients in group 1a and 1b differ in functionality, which means that e.g. patients in group 1b are bedridden >50% of time during a day compared to group 1a patients. Thus, patients in group 1a are considered to have no or only minor functional impairment. Patients in group 2 suffer from severe comorbidities leading to palliative care in case of pneumonia, whereas treatment is administered with a curative approach in patient groups 1a and 1b.
At initial assessment severity of CAP is assessed by calculation of the CRB65 score. The score is explained in table 6. In addition, oxygenation should be measured and unstable comorbidities must be detected. These parameters influence the decision of hospital admission, which is nonetheless a decision of the treating physician (12).

1.3 Diagnostic

1.3.1 Diagnoses of Community-Acquired Pneumonia

The diagnoses of CAP is based on thorough history, physical examination, appropriate laboratory tests and radiological procedures all described below. By combining the results obtained from the examination findings, the diagnosis of CAP can be made with certainty.

1.3.2 Clinical Symptoms

Clinical symptoms, indicative of CAP, can vary widely depending on age (23). The most common symptoms include cough (with or without sputum), chest pain, and dyspnea as well as fever, confusion and malaise. (Table 4) Elderly patients may even be oligosymptomatic. The absence of fever and cough, two aspects considered classic symptoms of pneumonia, is the case in up to 50% of patients (23).

Table 4: Symptoms of Pneumonia

General pulmonary as well as extrapulmonary symptoms of CAP from Ewig S. Anamnese, klinische Symptomatik und Untersuchungsbefunde. In: Ewig S, editor. Ambulant erworbene Pneumonie (23).

General symptoms of lower respiratory tract infection or severe sepsis.	Fever (temperature 38.3 C or (rarely) Hypothermia <36 C) Malaise Confusion
Pulmonary symptoms	Cough Sputum Dyspnea Chest pain
Extrapulmonary symptoms	Cephalgia Diarrhea limb and muscle pain Herpes labialis (especially in pneumococcal pneumonia)

1.3.3 Differential Diagnosis

In differential diagnosis, pneumonia must be distinguished from bronchitis or exacerbated COPD (24). This is important with regard to the administration of antibiotics. Likewise, bronchitis caused by Influenza viruses should be recognized in order to treat with virustatics . If an infiltrate is evident on chest x-ray, the suspected diagnosis of bronchitis can be ruled out (24).
In their article, Martin Kolditz et al. describe criteria that increase the pretest probability for the presence of an infiltrate from 5%-18% (25) if at least 2 of the following criteria are present:

- absence of rhinorrhea
- dyspnea and/or elevated respiratory rate
- focal abnormality in auscultation
- abnormal vital signs (fever, tachycardia >100/min)
- elevated biomarkers (e.g., C-reactive protein [CRP] >20–30 mg/L)

Other differential diagnoses include bronchial carcinoma, pulmonary tuberculosis, pulmonary embolism, and pulmonary fibrosis (24).

1.3.4 Clinical Examination Findings

Findings possibly obtained in physical examination are summarized in table 5. This findings also includes parameters that suggest sepsis, e.g. the quick SOFA score.
The qSOFA score includes values such as

- respiratory rate ≥22/min
- altered mentation
- systolic blood pressure ≤100 mmHg (26)

Based on these parameters, the risk of developing sepsis can be assessed, the more detailed SOFA score calculated and the assignment to ICU with certain treatments can be started immediately.

Table 5: Examination Findings

Possible examination findings that may be seen in CAP from Ewig S. Anamnese, klinische Symptomatik und Untersuchungsbefunde. In: Ewig S, editor. Ambulant erworbene Pneumonie (23).

General condition	Impaired or severely impaired
Vital function disorders	Tachypnoea (respiratory rate ≥16/min) Tachycardia (heart rate ≥100/min) Hypotension (RR systolic <90 mmHg and/or diastolic ≤60 mmHg)
Pulmonary findings	Inspiratory rales Bronchial breathing Physical signs of pleural effusion (attenuated breath sound or knock, negative vocal fremitus).

1.3.5 Indices

If the patient is suspected of having CAP, it is important to determine the severity of the condition so that treatment can be initiated quickly. Various scores and auxiliary parameters can be used for this purpose (e.g. CURB, CRB, CRB 65, PSI).

Table 6: CURB Index

Definition of CURB from Lim WS Defining community acquired pneumonia severity on presentation to hospital (27).

The CURB Index is composed of the following components
Confusion
Urea >7 mmol/l,
Respiratory rate >30/min
low systolic (<90 mmHg) or diastolic (<60 mmHg)

The CRB score includes the above mentioned criteria without urea; the CRB65 score is the CRB score with the additional criterion of age over 65 years.

For CURB and CRB65, 0-4 points can be achieved, and for CRB 0-3 points.

At 0 points, the mortality is about 1%, at 1-2 points, about 8-9%, at 3 or more points, about 22-31% (27).

T. T. Bauer et al. compared the 3 scores in relation to future deaths from CAP in both outpatient and hospital settings (28). They concluded that in both hospitalized and ambulatory patients, the CRB65 score should be preferred over the other two because it has better availability than the CURB score and achieves similar lethality prediction. The disadvantage of the CRB score is that it may lead to a lower risk classification in hospitalized patients due to rather low sensitivity (28).
In this context, the PSI by Michael J. Fine et al. can be used as a supplement or as an alternative (29). However, this score contains more values and is more difficult to determine than the CRB65 score.

1.3.6 Radiological Diagnostics

Both the S3 guidelines for CAP and Alexander Kaysin et al. recommend performing a chest x-ray (CXR), if CAP is suspected, or a chest sonography if an x-ray unit is not available (12, 30). A (new) infiltrate confirms the diagnosis of CAP (31). Furthermore, the CXR should be carried out in two different phases, as in one plane alone, the so-called "blind spot" can occur and, as a result, infiltrate rates in the retrocardiac area can be missed (31).
However, various studies showed weaknesses of CXR with limited sensitivity (32). Although the specificity for a chest radiograph to detect pneumonia was 93%, the sensitivity was only 65%.
High-resolution computed tomography would be the most sensitive method (23).

1.3.7 Microbiological Diagnostics

According to the S3 guidelines, microbiological diagnosis is not required for mild CAP, whereas for moderate to severe pneumonia of groups 1a and 1b, two blood culture pairs should be taken. For Legionella, a urine antigen test should be performed and sufficient sputum should be collected (12).

1.3.7.1 Blood Cultures (BC)

BC are a controversial topic, as new evidence continues to emerge questioning their usefulness. Andrew Lee et al. found that sensitivity can vary greatly with the number of BC. According to the authors, four BC should be taken to achieve 99% sensitivity. This result, however, only refers to bloodstream infections (33).
As claimed in current publications, bacteremia can be detected in only about 10% of obtained BC in patients with CAP (34, 35).
Both the IDSA/ATS guidelines and the S3 guidelines do not recommend BC in mild CAP because of poor evidence (12, 36).

The European guidelines recommend at least two pairs of BC bottles should be obtained in in moderate or severe CAP cases, whereas in American guidelines this should only be done if the following criteria apply (12, 36, 37):

1) Classified as severe CAP (see Table 7)
2) Empirically treated for MRSA or Pseudomonas aeruginosa
3) History of MRSA or Pseudomonas aeruginosa infection
4) History of intravenous antibiotic treatment in the last 90 days.

Table 7: Criteria for Severe CAP in America

Major and Minor Criteria for severe CAP in America from Metlay JP et al., Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia (36).

Minor Criteria
Respiratory rate ≥30 breaths/min
Multilobar infiltrates
Pa_{O2}/Fi_{O2} ratio ≤250
Confusion/disorientation
Uremia (blood urea nitrogen level ≥20 mg/dl)
Leukopenia (white blood cell count <4,000 cells/μl)
Thrombocytopenia (platelet count <100,000/μl)
Hypothermia (core temperature <36°C)
Hypotension requiring aggressive fluid resuscitation

Major Criteria
Septic shock with need for vasopressors
Respiratory failure requiring mechanical ventilation

Nima Afshar et al. conducted a systematic review and concluded that even BC are of little value in hospitalized patients. In the 13 studies, therapy changes were made according to a pathogen in 0-1% and antibiotic restriction occurred in 0-3% (38).
Moreover, the severity of the CAP should be considered when deciding whether or not to collect BC. This study came to the conclusion that BC should only be drawn in patients with a pneumonia severity score (PSI) of 4 or 5, in which a significant impact on therapy is anticipated (39). In another study the necessity and the validity of BCs in severe CAP or HCAP were investigated (40). The authors found that although severe pneumonia showed a higher incidence of bacteremia and the presence of a multidrug-resistant organism, in contrast to non-severe CAP. In addition, changes in therapy, mainly escalation of therapy, occurred in only 2% of cases.

1.3.7.2 Urine Antigen Test for Legionella

Toshihiko and Shimada conducted a systematic review and meta-analysis on the significance of urine antigen tests for Legionella (41). The authors concluded that the sensitivity was approximately 75%, and the specificity reached 100% in infections due to Legionella serotype 1.

1.3.7.3 Sputum Staining and Culture

According to S3 guidelines, adequate sputum, which should be processed in a time frame of 2-4h for culture and Gram stain, should be used. If the above criteria cannot be met, sputum examination is not necessary (12).
Nevertheless, there is ongoing discussion regarding the usefulness of sputum culture (42-46).

1.4 The Most Common Pathogens

Streptococcus pneumoniae

Pneumococci are bacteria belonging to the group of streptococci (47).

Occurrence: The pathogen occurs in both animals (e.g. rats, monkeys) and humans. Unencapsulated strains colonize the pharyngeal mucosa in 40-70% of people, but are not infectious due to their nature (unencapsulated).

Epidemiology: Pneumococci can cause meningitis in both adults and children. Furthermore, they are a leading cause of death in developing countries by causing pneumococcal pneumonia.

Infection Route: Routes of transmission between humans are usually rare, most likely traceable to endogenous infection.

Clinical presentation: Clinical manifestations with this pathogen are often lobar or bronchopneumonia.

Prevention: Vaccination (47).

Haemophilus influenzae

Haemophilus influenzae, a species of the genus Haemophilus in the Pasteurellaceae family, is a gram-negative, partly coccoid, partly filamentous, pleomorphic rods bacterium (48).

Occurrence: The only known reservoir of the pathogen is humans, with approximately 50% of them being colonized by the pathogen.

Epidemiology: Worldwide, about 3 million people suffer from a Haemophilus infection.

Infection route: The pathogen can be transmitted via droplets (e.g. coughing, sneezing) or smear infection.

Clinical presentation: Diseases that can be caused by the germ include meningitis, epiglottitis (capsule type B), otitis media, sinusitis, bronchitis, pneumonia, conjunctivitis.

Prevention: Vaccination (48).

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a bacterium and belongs to the Mycoplasmataceae group. Together with other germs such as Legionella spp. and Chlamydophila pneumoniae, they form the group of atypical pneumonia pathogens (49, 50).

Occurrence: Mycoplasma pneumoniae reside solely in humans.

Epidemiology: The germ is widespread worldwide and preferentially affects younger people; likewise, regardless of age, it is often associated with superinfection. An epidemic can be expected every 3-7 years, which also has the potential to become a pandemic and spread across continents.
Infection route: The route of transmission is also via droplet infection, increasingly in rooms where many people gather in a confined space.
Clinical presentation: Clinically, Mycoplasma pneumoniae often presents as tracheobronchitis, although interstitial pneumonia may also be present in 5-10% of cases. At the beginning of the disease, typical symptoms such as fever, headache or a strong feeling of illness, are absent and only an increasingly strong, irritating cough as well as a, small, glassy, viscous sputum, can be indications of Mycoplasma pneumoniae. Chlamydial infections, Q fever, Legionella infections, and especially viral pneumonias should also be considered for differential diagnosis.
Prevention: Vaccination not available (50).

Chlamydia

Chlamydia spp. (Chlamydophila spp.) are a group of gram-negative, obligate intracellular bacteria that can be divided into 3 groups, with Chlamydia pneumoniae being the most common causative agent of pneumonia (51).
Occurrence: Humans are basically the main reservoir, but pathogens have also been detected in animals (52).
Epidemiology: Both endemics and epidemics can be caused by the pathogen. Classically, children are affected by this disease, with 60% having had contact with the germ by the age of 20.
Infection route: The typical route of transmission is aerogenic.
Clinical presentation: Bullous myringitis, otitis, and mild non-exudative pharyngitis are common manifestations of upper respiratory tract mycoplasma infection (53).
Patients who had chlamydia pneumonia were more likely to suffer from headaches as well as laryngitis (53, 54).
Prevention: Vaccination not available (51).

Influenza

Influenza virus can be categorized into 3 groups (A, B, C) and belong to the orthomyxoviruses (55).

Epidemiology: The flu epidemic affects millions of people worldwide every year. Both antigenic drift and antigenic hit form the basic components for this.

Infection route: As with bacteria, viruses are mainly transmitted by droplet infection, for example: talking or sneezing, likewise they can also enter the respiratory tract through contaminated hand.

Clinical presentation: Influenza virus infection can be symptomatic or asymptomatic. There is a distinction between purely viral pneumonia and super bacterial pneumonia caused by bacteria. Viral infections are still more common in children, although they can, of course, also affect adults (56). The British Thoracic Society guidelines argue that the following symptoms: fever >38.5°C, respiratory rate >50 breaths/min, chest recession could be more suggestive of a bacterial etiology; whereas wheezing, fever <38.5°C, and striking chest recession, could be more indicative of viral infection (56). However, a clear-cut classification is not possible because bacterial and viral symptoms may overlap.

Prevention: Vaccination (55).

Staphylococcus aureus

Staphylococci are gram-positive, facultatively anaerobic bacteria. The specificity of Staphylococcus aureus is the formation of free coagulase, this feature distinguishes it from the other species (57).

Occurrence: In humans, the germ frequently colonizes the skin and areas such as the nasal vestibule, perineum, vagina or rectum. A peculiarity that characterizes this germ is the resistance position. In general, penicillins are the primary therapy; but in recent years, high levels of resistance have been encountered, so that their efficiency is only about 20% (58).

Epidemiology: Staphylococcus aureus can cause a wide range of diseases, including wound infections, osteomyelitis, endocarditis, sepsis, staphylococcal scalded skin syndrome, impetigo contagiosa, toxic shock syndrome, and 10% of pneumonia.

Infection route: The ways of germ transmission include smear infections as well as self-infections.

Clinical presentation: Local infections, sepsis, or toxin-related syndromes reflect the clinical manifestation of Staph. aureus infection.

Prevention: There is no vaccination; therefore, people working in health care should disinfect their hands thoroughly before and after patient contact, before aseptic activities, and after contact with potentially infectious material (57).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a gram negative, facultative aerobic bacterium.

Occurrence: The hallmark is its high environmental resistance as well as its preference for humid areas (for example: sinks, ventilation hoses, humidifiers, sewage Pipes, incubators, etc.). In humans, the Pseudomonas spp. can be found in the throat and nose (59).

Epidemiology: Nosocomial pneumonias are frequently caused by this pathogen, as are urinary tract infections, wound infections, sepsis, and otitis externa/media. This study vividly demonstrates that only about 4% of CAP is due to Pseudomonas aeruginosa, with previous infection/colonization, tracheostomy, bronchiectasis, IRVS, and very severe COPD being risk factors (60).

Infection Route: Infection occurs either by direct transmission between patients or is picked up from the environment.

Clinical Presentation: Ventilated patients may develop lower respiratory tract infections, furthermore wound and urinary tract infections may occur.

Prevention: Vaccination is not yet available. Cleaning of contaminated equipment, careful disinfection of hands, and filtration systems for water pipes are the most important preventive measures to avoid occurrence or spreading (59).

Klebsiella pneumoniae

Klebsiella are gram-negative, rod-shaped bacteria that belong to the Enterobacteriaceae group (61).

Occurrence: The pathogen is found in the stool of 5-38% of people; 1-6% of people also carry the germ in the nasopharynx (62).

Epidemiology: In CAP, the morbidity rate due to this pathogen is about 3-5% in Western countries (62).

Infection Route: This germ is also transmitted directly from person to person, through contaminated blood supplies, infusions or through food.

Clinical presentation: Clinically, the pathogen often manifests as urinary tract infection, pneumonia, severe soft tissue infection, sepsis, and exacerbation of chronic bronchitis.

Prevention: Vaccination not available (61).

Escherichia coli

Escherichia coli belongs to the group of gram-negative bacteria .

Occurrence: The typical colonization area of the germ is the intestine of humans and animals (61).

Infection Route: Transmission may occur through the consumption of meat products (63).

Clinical presentation: The pathogen can cause urinary tract infections, wound infections, peritonitis, appendicitis, cholecystitis/cholangitis, and sepsis, when germs migrate from the intestine to the corresponding parts of the body.

Prevention: Vaccination not available (61).

1.5 Therapy

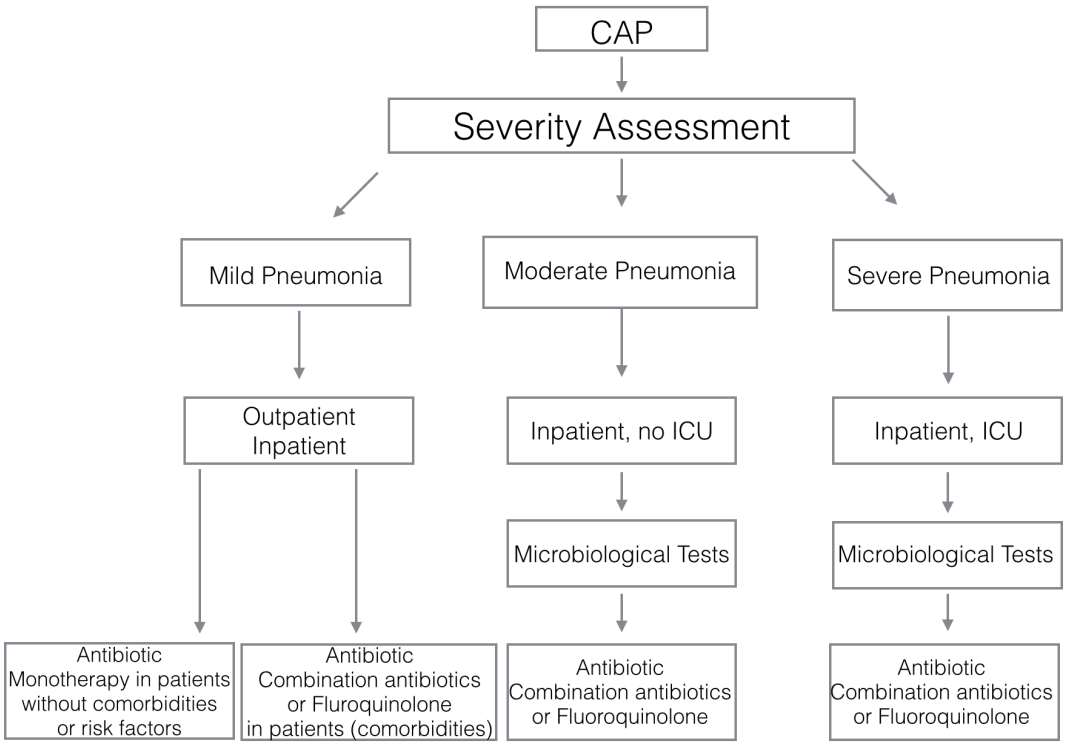
According to the recently published S3 guideline (LIT) the treatment of CAP is based on the assignment of patients to outpatient or inpatient treatment. Treatment options are shown in table 9. The timeframe between diagnosis and initiation of antibiotic treatment impacts outcome. Thus, it is recommended to administer antibiotic treatment within 4 hours after diagnosis. Due to local resistance rates antibiotic therapy has to be adopted to these local circumstances. (64)

Table 8: Severity Classification of CAP

Criteria for the severity of CAP from Ewig S, Kolditz M, Pletz M, Altiner A, Albrich W. Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie – Update 2021 2021 (64)

Mild pneumonia	CRB65 = 0 normal or compensated oxygenation no decompensated comorbidity
Moderate pneumonia	1-2 Minor Criteria unstable comorbidity Lactate >2mmol/L
Severe pneumonia	>2 Minor Criteria or systemic hypotension with vasopressor therapy or ventilation

Figure 1: Flow Chart for Selection of Antibiotic Treatment



Classification based on severity with associated therapy inspired by Prina E et al., CAP (65).

Table 9: Antibiotic Therapy of the Different Pneumonia Severities

Therapy of Cap from Ewig S, Höffken G, Kern WV, Rohde G, Flick H, Krause R, et al. Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie und Prävention – Update 2016 (12)

Severity	First Line therapy	Alternative therapy
Mild pneumonia without comorbidities (oral therapy)	Amoxicillin	Moxifloxacin, Levofloxacin Clarithromycin, Azithromycin Doxycyclin
Mild pneumonia with comorbidity (oral therapy) - Chronic heart failure - CNS disorders with dysphagia - Severe COPD, bronchiectasis - bedriddenness, PEG	Amoxicillin/Clavulanate	Moxifloxacin, Levofloxacin
Moderate pneumonia	Amoxicillin/Clavulanate* Amoxicillin/Sulbactam* Cefuroxim* Ceftriaxon* Cefotaxim*	Moxifloxacin, Levofloxacin
Severe pneumonia	Piperacillin- tazobactam^ Ceftriaxon^ Cefotaxim^	Moxifloxacin, Levofloxacin

*+- macrolide for 3 days
^+ macrolide for 3 days

2 Methods

The aim of this diploma thesis is to investigate the incidence and etiology CAP and bacteremia in CAP in different European countries through a comprehensive review of the existing literature.

For the first part of the work, reference books, current guidelines as well as articles from electronic databases were consulted. PubMed and Google Scholar databases were used to search for studies and scientific articles.
For this purpose, search terms such as “incidence”, “etiology”, “bacteremia”, “pathogen spectrum”, and “bloodstream infection”, were entered for the respective country.
The results were then screened for relevance and adopted for this work.

In selecting the countries, attention was paid to Austria’s neighboring countries, which offer a good data basis in relation to the guiding question and represent Europe in the broader sense.

3 Results

3.1 Incidence and Etiology of Community-Acquired Pneumonia in European Countries

A summary of data mentioned below is provided in tables 10,11.

3.1.1 Germany

Since 2005, data have been evaluated at regular intervals by the Federal Agency for Quality Assurance (BQS) and detailed information on the incidence of CAP has been published (66). Approximately 290000 cases of CAP requiring hospital treatment were surveyed by the QS procedure in Germany in 2019 (67) .

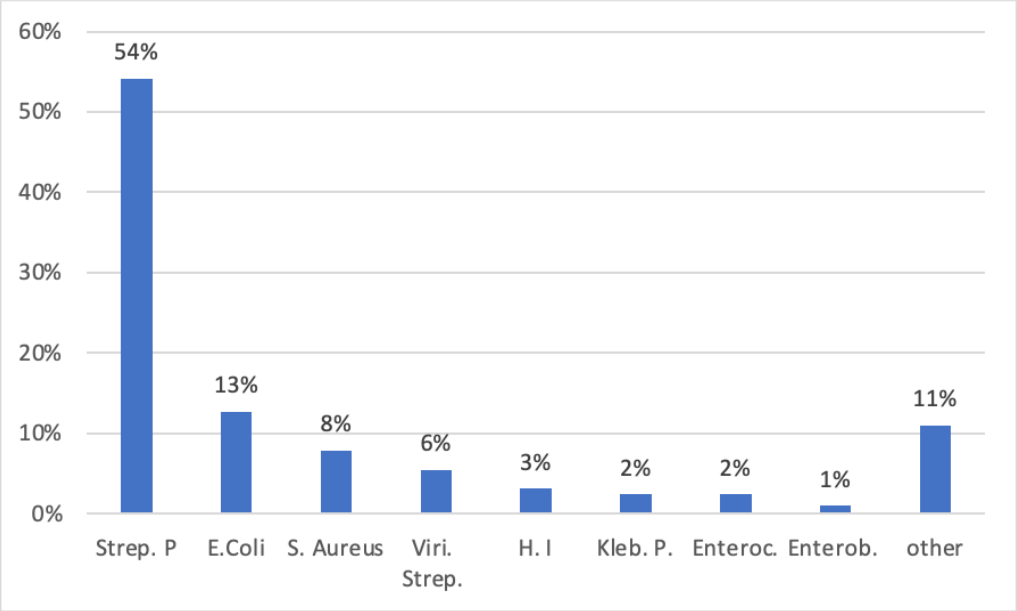
Based on data from health insurance companies, a CAP incidence of 9.7 cases per 1000 person can be assumed, which means 660000 patients per year (25). This result can be derived from a study that examined patients from 2010-2011 (68). The 9.7/1000 CAP incidence is composed of 4.5 hospitalized and 5.2 outpatients with CAP. Previous studies show similar results, with the difference that there was no distinction between outpatients and hospitalized CAP patients (69). Incidence also varies widely due to lack of patient populations, formulas as well as inclusion and exclusion criteria.
Furthermore, the 2018 statistics show a correlation between age and incidence (67).

Considering patients in the Capnetz cohort who tested positive for pathogens, 40% of participants were found to have Streptococcus pneumonia. Haemophilus influenzae and Mycoplasma pneumoniae were found in about 8%, influenza A virus in 6%, Staphylococcus aureus as well as E. coli in 4-5% of cases (70). The prevalence of Legionella was 3% and was associated with increased excess mortality. Enterobacter infections accounted for only a small proportion (<5%) and were predominantly detected in elderly people or persons in nursing homes suffering from comorbidities. The pathogens were detected by purulent sputum as well as by positive BC (70).
H. von Baum et al. took a closer look at blood and sputum cultures with regard to Enterobacter and Pseudomonas aeruginosa. Enterobacter was detected in 1.3%, Pseudomonas aeruginosa in 0.4% of cases (71).
The pathogen Mycoplasma pneumoniae was detected more often in younger patients (10, 11).

The prevalence of the pathogen decreased with increasing age, from 38% in 18-29 year olds to 13% for ≥60 year olds. In principle, women are more frequently tested positive for the pathogen than men, with the exception of patients between the ages of 18 and 29 (10). Similarly, Haemophilus influenzae represented an important pathogen, associated with patients who had been vaccinated against pneumococcus and had respiratory comorbidities (72).

Christina Forstner et al. examined BC for different pathogen spectra in patients with CAP. In total, approximately 8% of the BC were positive (73).

Figure 2: Pathogens Isolated in Blood Cultures in Germany from 292 Patients with CAP



Strep. P = Streptococcus pneumoniae, S. Aureus = Staphylococcus aureus, E.coli = Escherichia coli, H. I = Haemophilus influenzae, Enterob. = Enterobacter, Kleb. P.= Klebsiella, Viri. Strep. = Viridans Streptococcus, Enteroc. = Enterococcus
Forstner C. et al., Rate and Predictors of Bacteremia in Afebrile Community-Acquired Pneumonia (73).

In Germany, Streptococcus pneumonia (54%) was detected most frequently, followed by Escherichia coli (13%), Staphylococcus aureus (8%), Viridans streptococci (6%), Haemophilus influenzae (3%), Klebsiella (2%), Enterococcus (2%), Enterobacter (1%) and other (11%) (73).

3.1.2 France

The latest data on CAP comes from a French company called Cegedim Strategic Data that studies medical health care. In 2011 and 2012, a prospective cohort study (CAPA study) and an ancillary survey (AIMSIS) were conducted with the aim of estimating the CAP incidence in the French population. 425 family physicians agreed to include patients older than 18 years, who visited their practice with CAP, in the study. The auditors were either members of an FP network or they were engaged in FP teaching activities. To obtain a representative sample, the method of stratified random sampling was applied (74).

Inclusion criteria included: an age of at least 18 years, fever greater than 38.5 degrees, symptoms suggestive of pneumonia, chest pain, tachycardia >100 beats per minute, >25 breaths per minute, a history of unilateral crackles on auscultation, and/or shadowing on a radiograph of the chest. Similarly, NHAP patients were included (74).

One prospective study allows an adequate estimate of the incidence in France, based on a network of 425 FP proportionally divided according to the department's FP demography (74).
The study showed a CAP incidence of 4.7 per 1000 inhabitants, 18 years and older, and a CAP incidence of 6.7/1000 for inhabitants over 65 years old (74).
Comparisons of results with previous studies showed a CAP incidence of 1.8; however, the inclusion criteria were different as well as the patient population (75).

In 2015, a large-scale French study was conducted on the distribution and antimicrobial susceptibility of bacteria from adults with CAP or complicated skin and soft tissue infections. This study also examined the etiology of CAP nationwide (76).
The pathogens were extracted from samples of patients older than 18 years, and no patients with a diagnosis of NCAP were included (76).
The only pathogen isolate either came from sputum, bronchoscopic lavage, tracheal aspirate, brush specimen, BC, or from pleural fluid.
From these pathogen samples, Streptococcus pneumoniae (46%) was detected most frequently, followed by Haemophilus influenzae (15%), Staphylococcus aureus (13%), Enterobacteria (12%), and Branhamella catarrhalis (5%) (76).

This study showed that bacteremia episodes occurred in only approximately 9.4% of cases (77). Streptococcus pneumoniae as well as Haemophilus influenzae could be detected in patients with bacteremia.

3.1.3 Italy

A study was conducted that collected and interpreted results from the Health Search Database (HSD), which included data from 800 general practitioners (78). This study also demonstrated a correlation between age and incidence. People over the age of 85, who suffered from chronic diseases, were many times more likely to develop the disease than people around the age of 50.

Patients had to be at least 15 years of age or older and had to have had a diagnosis of CAP for 2 years, as defined by ICD9 (78).
The study provided area-wide data on the incidence of CAP in Italy. Based on 12704 individuals who took part in the study, in 2005, an incidence of 2.93 cases per 1000 inhabitants could be inferred. In 2009, the incidence increased to 3.06 cases per 1000 inhabitants. Lower incidence was found in previous studies (79, 80). This discrepancy could be due to the definition of CAP or the exclusion of patients younger than 15 years of age (78).

For Italy, no etiology of CAP could be ascertained due to low data availability. There was just one study found, describing the etiology of CAP in children in Tuscany (81).

The study examined data from hospitalized children under 18 years of age, who were diagnosed with pneumonia, between the years 1999 and 2009 (81).
The following bacteria were detected in those 5450 children: Mycoplasma pneumoniae (44.92%), Streptococcus pneumoniae (39.48%), influenza virus (15.42%), RSV (3.55%), Staphylococcus aureus (3.45%) and Klebsiella (1.72%) (81).

3.1.4 United Kingdom

In 2013, a study was published explaining the incidence of CAP in people over 65 years of age in the United Kingdom (82). The incidence was assessed using information from approximately 8% of the population. Data on gender, age, and geographic distribution were used anonymously only and were representative of the population.

Included were patients aged 65 years or older, between April 1997 and March 2011, who met the inclusion criteria developed by a committee consisting of a respiratory specialist, a general practitioner, and an epidemiologist (82).

In a patient collective of 58,772 cases an increase in CAP incidence between the years 1997 and 2011 was shown. In 1997, the incidence rate for those aged 65-69 years was 2.59, but in 2010 it was 3.61/1000. In general, the incidence rate increased among all age groups between the years mentioned above (82).

A prospective study conducted in 1986 in Nottingham showed similar results in terms of pathogens in comparison to other European countries (83). Sputum, blood, pleural fluid, postmortem lung tissue, and throat swabs were evaluated. The most common bacteria were Streptococcus pneumoniae with 36%, followed by Haemophilus influenzae with 10%, and Mycoplasma pneumoniae with 1%. Viruses also accounted for a fairly large proportion at 13%. Staphylococcus aureus and Escherichia coli were found in about 1% of the participants (83). Thirteen years later, WS Lim et al. performed another study with subjects from Nottingham Hospital (84). The most common bacterial pathogen was again Streptococcus pneumoniae (48%), followed by Chlamydia pneumoniae (13%), Haemophilus influenzae (7%), Mycoplasma pneumoniae (3%), Legionella pneumophilia (3%), Chlamydia spp. (2%), Moraxella catarrhalis (2%), and Coxiella burnetii (0.7%). The influenza type A virus was present in 19% of subjects. BC achieved a positivity rate of 8%; Staphylococcus aureus, Klebsiella, and Escherichia coli were extracted from these BC (84).

3.1.5 Spain

From 2009 to 2013, a retrospective observational study was conducted in Spain to determine the incidence of CAP (85). Data were obtained and interpreted from a large database called BIFAP. A total of 2,692 physicians from different specialties such as general practitioners, pediatricians, etc. provide this database with relevant information that can be used for studies.

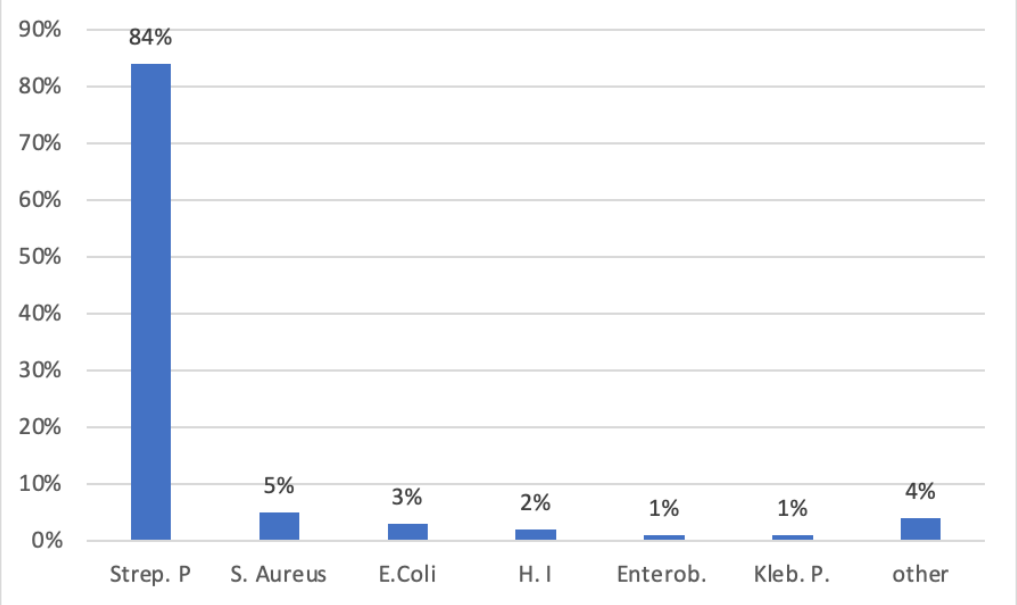
An inclusion criterion for this study was an age of 18 years and older; both male and female subjects were included. Study participants were also required to receive a diagnosis of CAP between the years 2009 and 2013, either made by a physician, medical professional, and/or radiologist (85).

In total, the results of 2,332,622 patients could be used. The results of the study showed an incidence rate of 4.63 per 1000 person years and a correlation between age and incidence. While the incidence rate for 18- to 20-year-olds was 1.98, it was significantly higher for those over 90 years of age, with a rate of 23.74. As for gender, the results between women and men aged 20-65 were almost the same, with a rate of 1.47-5.2. More men appeared to be affected in the group of people aged 65 or older, which is also evident in other studies (85-87). Compared to previous studies, there was an increase in incidence (88, 89). The reason why the incidence differs from previous studies may be due to inclusion criteria, differences in health care systems as well as the definition of CAP.

Over the years, several studies have been published in Spain, allowing the country to contribute a variety of results on the etiology of CAP. In 2003, for instance, a multicenter study involving 16 hospitals was published. The study included people 65 years and older. In this context, germs were found in 40% of the participants listed in the following in order of frequency. Streptococcus pneumoniae (49%), atypical pathogens and viruses accounted for 20%, Haemophilus influenzae (14%), and Legionella pneumophila (8%) (90).
In 2010, a prospective study including patients with CAP admitted between 1996 and 2008 was published (91). The most common etiologies were Streptococcus pneumoniae with 42%, followed by atypical pathogens (Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, and C. burnetii) with 18%. Viruses accounted for a percentage of 10%, Haemophilus influenzae was detected in 5%, and Pseudomonas aeruginosa in 3%.

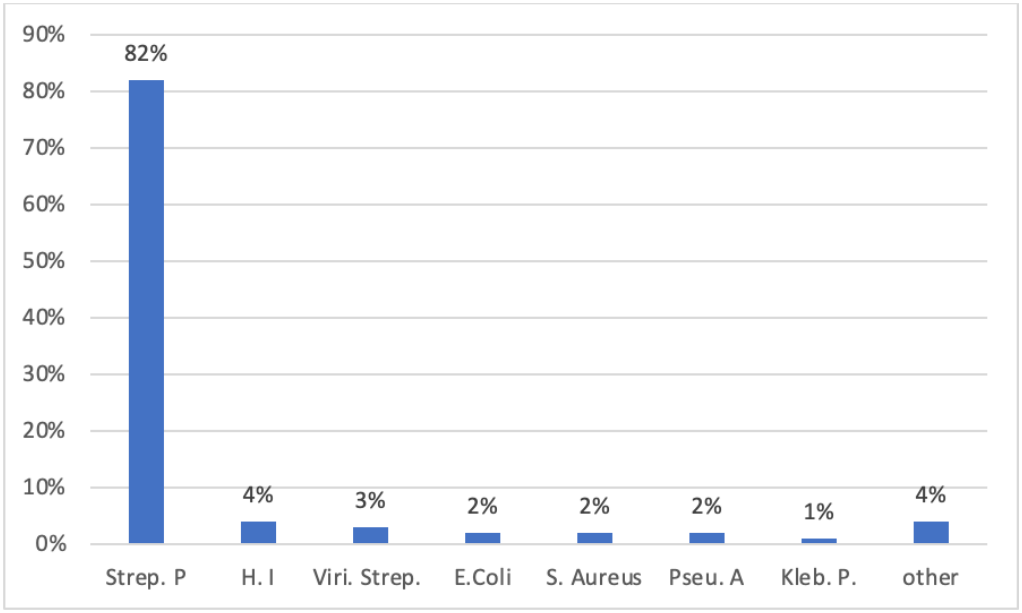
Another study was conducted in Barcelona regarding pathogens in BC. A bacteremia episode was detected in only 10% of cases. Streptococcus pneumoniae was the most common pathogen isolated in bacteremia patients with (84%), followed by Staphylococcus aureus with (5%), Escherichia coli with (3%), and Haemophilus influenzae with (2%) (35). Catia Cillóniz et al. also studied bacteremia in outpatients with CAP with the result that Streptococcus pneumoniae was most frequently detected at 92%, followed by Haemophilus influenzae at 8% (92).
Miquel Falguera et al. likewise showed that Streptococcus pneumoniae was the most common pathogen with 82%, followed by Haemophilus influenzae with 4%, and viridans streptococci with 3%; Staphylococcus aureus, Pseudomonas aeruginosa as well as Escherichia coli were each 2%, and Klebsiella pneumoniae was 1% (93).

Figure 3: Pathogens Isolated in Blood Cultures in Spain from 297 Patients with CAP



Strep. P = Streptococcus pneumoniae, S. Aureus = Staphylococcus aureus, E.coli = Escherichia coli, H. I = Haemophilus influenzae, Enterob. = Enterobacter, Kleb. P.= Klebsiella
After Torres A et al., Bacteremia and antibiotic-resistant pathogens in community acquired pneumonia: risk and prognosis. European Respiratory Journal (35)

Figure 4: Pathogens Isolated in Blood Cultures in Spain from 322 Patients with CAP



Strep. P = Streptococcus pneumoniae, S. Aureus = Staphylococcus aureus, E.coli = Escherichia coli,
H. I = Haemophilus influenzae, Viri. Strep. = Viridans streptococcus,
Kleb. P.= Klebsiella, Pseu. A = Pseudomonas aeruginosa
After Falguera M et al., Prediction Rule for Estimating the Risk of Bacteremia in Patients with Community-Acquired Pneumonia. Clinical Infectious Diseases (93).

The pathogens which were obtained exclusively from BC in Spain were composed as follows. Streptococcus pneumoniae ranked first (82-92%), followed by Staphylococcus aureus (2-5%), Escherichia coli (2-3%), Haemophilus influenzae (2-8%), Pseudomonas aeruginosa (2%), Enterobacter (1%), and Klebsiella (1%) (35, 93).

3.1.6 Sweden

P. Naucler et al. conducted a nationwide register-based study in Sweden regarding the incidence of CAP using data provided by the National Patient Registry (NPR) and the National Board of Health and Welfare (94).

Both young and old patients diagnosed with pneumonia were included. These people were then divided into different age groups. The period of investigation covered the years 2005 to 2015. There were 303,691 episodes of CAP detected. According to study results, the incidence increased from 1,4 to 1,6 (40-64 years), 4,7 to 5,7 (65-74 years) and 11,9 to 13,7 (75-84 years) (94).

Based on this study, it can be concluded that in Sweden the most common bacterial pathogen is S. pneumonia (39%), followed by Haemophilus influenzae (5%), and Mycoplasma pneumoniae (5%) (95). An outlier, regarding Haemophilus influenzae, is shown by the study of F. Lagerström et al., where the germ accounted for 14-28% of the people examined. According to the authors, this difference is due to smokers, since they are more likely to develop chronic bronchitis, which is often caused by the germ Haemophilus influenzae (96).

Table 10: Incidence of CAP in Different European Countries

Country	Study Period (Reference)	Age group	Annual Incidence
Germany	2003 (69) *	>18	3,7 – 10
	2010-2011 (68) +	>18	9,7 (4,5 H, 5,2 O)
Bacteremia Episode	8% (73)		
France	1993-1994 (75) 2011-2012 (74) +	>3 ≥18 ≥65	1,8 4,7 6,7
Bacteremia Episode	9,4% (77)		
Italy	1997-1999 (80) *	<65 ≥65	0,78 4,8
	1999-2000 (79) *	≤14 15-44 45-64 >64 All Ages	0,7 0,9 1,6 3,3 F: 1,7 M: 1,7
	2005-2009 (78) *	≥15	2.93-3,06
United Kingdom	1997-2011 (82) +	65-69 70-74 75-79 80-84 85-89 All Ages	2,2-3,6 3,4-5 6,0-7,8 9,4-13,4 16,6-21,5 F: 7,53 M: 8,6
Bacteremia Episode	8% (84)		
Spain	1993-1995 (89) *	15-39 40-64 >64	F: 1,0 M: 1,2 F: 1,4 M: 1,8 F: 1,9 M: 5,2
	1999-2001 (88) +	15-44 45-64 65-74 >75	F: 0,58 M: 0,77 F: 0,74 M: 1,43 F: 1,64 M: 3,22 F: 3,0 M: 8,72
	2002-2005 (87) +	65-74 75-84 ≥85	F: 2,18 M: 2,99 F: 2,76 M: 5,29 F: 7,92 M: 9,99
	2002-2005 (86) +	65-74 75-84 ≥85	8,6-11,4 14,6-19,4 23,5-36,2
	2009-2013 (85) +	18-20 60-65 80-85	F: 1,5 M: 2,5 F: 5,2 M: 5,8 F: 9,6 M: 19,4
Bacteremia Episode	7-10% (35, 92)		
Sweden	2005-2015 (94) +	40-64 65-74 75-84	1,4-1,6 4,7-5,7 11,9-13,7

H = Hospitalized, O = Outpatient, F = Female, M = Male

*Cases per 1000 population, + Cases per 1000 person- years, – 10 year incidence

Table 11: Comparison of the Etiology of CAP Between Countries
Pathogens of CAP (detected in sputum, BC, tracheobronchial aspirate, bronchoscopic lavage, etc.)

	Germany (70, 71)	France (76)	Italy* (81)	UK (83, 84)	Spain (90, 91)	Sweden (95)
Strep. P.	40%	46%	39,48%	36-48%	42-49%	39%
H. I	8%	15%	-	7-10%	5-14%	5%
Myco. P.	8%	-	44,92%	1-3%	1-18%	5%
Viruses	6%	-	15,42%	13-19%	10-20%	5%
S. Aureus	4-5%	13%	3,45%	1%	-	1%
E. Coli	4-5%	-	-	1%	-	-
Legionella	3%	-	-	3%	8-18%	1%
Enterob.	1%	12%	-	-	-	-

* Children <18 years
Strep. P = Streptococcus Pneumoniae, H. I = Haemophilus influenzae,
Myco P. = Mycoplasma pneumoniae, S.. Aureus = Staphylococcus aureus,
E.coli = Escherichia coli

Streptococcus Pneumoniae (36-49%) was the most common pathogen in the countries indicated, followed by Haemophilus influenzae (5-15%), Mycoplasma pneumoniae (1-45%), Staphylococcus aureus (1-13%), Legionella (1-18%), Escherichia coli (1-5%), and Enterobacter (1-12%). Viruses were also quite common (5-20%).

4 Discussion

The aim of this literature review was to collect and interpret data from European countries on the incidence and etiology of patients with CAP and bacteremia in CAP. However, some limitations were encountered during the search.

First, there were only a limited number of studies that were eligible for evaluation of etiologic agents causing bacteremia in patients with CAP. Regarding the etiology in CAP in most studies, the etiologic pathogens presented were not only obtained from BC. Therefore, the spectrum of pathogens varies widely and cannot be attributed solely to bacteremia in BC.

The second limitation relates to the countries studied. While some countries conducted multiple studies on bacteremia in CAP patients, others provided no studies at all in this regard. The interpretation of the study results is equally difficult, as in some countries several results had to be compared, whereas in other countries only individual studies had to be interpreted. As a result, the results vary from country to country.

A third limitation is, among other things, the evaluation of the results. For example, if two pathogens were detected in BC, it was not clear in some studies what the percentage distribution of these was.

While in some studies the most common pathogen was included in the results, other studies reported both pathogens, leading to results above 100%. In the absence of a uniform study design, it was difficult to understand and correctly interpret results. Similarly, it should be questioned whether the pathogen detected is actually the cause of CAP or whether it is just contamination.

Fourth, as described in the introduction, it is important to take at least four BC to ensure 99% sensitivity. If fewer BC are used, the sensitivity decreases. Again, studies did not provide explicit data on the number of BC taken.

Regarding the pure incidence of bacteremia, most studies concluded that bacteremia could be detected in about 7-10% of BC.

In BC, the most common pathogen was by far Streptococcus pneumoniae, followed by Escherichia coli, Staphylococcus aureus, and Haemophilus influenzae. Compared to the pathogens which were not exclusively obtained from BC, there was a shift in frequency of Haemophilus influenzae.

Similarly, the pathogen Mycoplasma pneumoniae was not detected in BC but was detected in cultures from different types of samples (sputum, blood, tracheobronchial aspirate, bronchoscopic lavage, etc.). Mycoplasma pneumoniae was found more frequently in younger patients. In the German study of bacteremia in CAP patients, the pathogen E.coli was detected much more frequently (13%) than in the Spanish studies. The reason for this is not known. The authors also agreed with the S3 guidelines to draw BC only in hospitalized patients because of the low bacteremia rate in outpatients with CAP. Nevertheless, the frequency of pathogens is approximately equally distributed in the different European countries.

Based on these results, it can be concluded that antibiotic therapy, as suggested in the guidelines, can also be applied to a lot of the pathogens extracted from BC.
In spite of this, attention should be paid to the Staphylococcus aureus germ, as it might show resistance to standard therapy in case of methicillin resistance, which varies between European countries. Despite the low positivity rate BC add to the detection of etiologic agents enabling adjustment of therapy as needed.
Still, caution should be exercised in interpretation of available data regarding bacteremia in CAP, as only a few validated studies were found. Due to the paucity of studies, only limited evidence can be presented on the usefulness of BC.

5 References

1. Ewig S, Phillipou S. Pathologie und Komplikationen. In: Ewig S, editor. Ambulant erworbene Pneumonie. Bochum: Springer-Verlag Berlin Heidelberg; 2016. p. 17-24.
2. Randerath W. Pneumonien. In: Herold G, editor. Innere Medizin. Köln: Herold, Gerd; 2018. p. 372-88.
3. Reynolds JH, McDonald G, Alton H, Gordon SB. Pneumonia in the immunocompetent patient. Br J Radiol. 2010;83(996):998-1009.
4. Tarver RD, Teague SD, Heitkamp DE, Conces DJ, Jr. Radiology of community-acquired pneumonia. Radiol Clin North Am. 2005;43(3):497-512, viii.
5. Ewig S. The pneumonia triad. Community-Acquired Pneumonia Eur Respir Monogr. 2014;63:13-24.
6. Ott SR. Ambulant erworbene und nosokomiale Pneumonie. Swiss Medical Forum. 2018;18(26-27):569-74.
7. Ewig S. Definitionen. In: Ewig S, editor. Nosokomiale Pneumonie. Bochum: Springer-Verlag GmbH Deutschland; 2017. p. 1-6.
8. Ewig S. Definitionen. In: Ewig S, editor. Ambulant erworbene Pneumonie. Bochum: Springer-Verlag Berlin Heidelberg; 2016. p. 1-7.
9. Miyashita N, Ouchi K, Kawasaki K, Oda K, Kawai Y, Shimizu H, et al. Mycoplasma pneumoniae pneumonia in the elderly. Med Sci Monit. 2008;14(8):Cr387-91.
10. Dumke R, Schnee C, Pletz MW, Rupp J, Jacobs E, Sachse K, et al. Mycoplasma pneumoniae and Chlamydia spp. infection in community-acquired pneumonia, Germany, 2011-2012. Emerg Infect Dis. 2015;21(3):426-34.
11. Klapdor B, Ewig S, Pletz MW, Rohde G, Schütte H, Schaberg T, et al. Community-acquired pneumonia in younger patients is an entity on its own. Eur Respir J. 2012;39(5):1156-61.
12. Ewig S, Höffken G, Kern WV, Rohde G, Flick H, Krause R, et al. Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie und Prävention – Update 2016 2016 [Available from: <020-020l_S3_ambulant_erworbene_Pneumonie_Behandlung_Praevention_2016-02-2.pdf>.
13. Ewig S, Klapdor B, Pletz MW, Rohde G, Schütte H, Schaberg T, et al. Nursing-home-acquired pneumonia in Germany: an 8-year prospective multicentre study. Thorax. 2012;67(2):132-8.

14. Maruyama T, Gabazza EC, Morser J, Takagi T, D'Alessandro-Gabazza C, Hirohata S, et al. Community-acquired pneumonia and nursing home-acquired pneumonia in the very elderly patients. Respir Med. 2010;104(4):584-92.
15. Kang YS, Ryoo SR, Byun SJ, Jeong YJ, Oh JY, Yoon YS. Antimicrobial Resistance and Clinical Outcomes in Nursing Home-Acquired Pneumonia, Compared to Community-Acquired Pneumonia. Yonsei Med J. 2017;58(1):180-6.
16. Chalmers JD, Rother C, Salih W, Ewig S. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clin Infect Dis. 2014;58(3):330-9.
17. Ewig S, Welte T, Chastre J, Torres A. Rethinking the concepts of community-acquired and health-care-associated pneumonia. Lancet Infect Dis. 2010;10(4):279-87.
18. Bartlett J. Aspiration pneumonia. Netter's Infectious Disease: Elsevier Inc.; 2011. p. 153-6.
19. Makhnevich A, Feldhamer KH, Kast CL, Sinvani L. Aspiration Pneumonia in Older Adults. J Hosp Med. 2019;14(7):429-35.
20. Geerdes-Fenge HF. [Travel-associated pneumonias]. Pneumologie. 2014;68(10):685-95.
21. Shi Y, Wang G, Cai XP, Deng JW, Zheng L, Zhu HH, et al. An overview of COVID-19. J Zhejiang Univ Sci B. 2020;21(5):343-60.
22. Porten K, Rissland J, Tigges A, Broll S, Hopp W, Lunemann M, et al. A super-spreading ewe infects hundreds with Q fever at a farmers' market in Germany. BMC Infect Dis. 2006;6:147.
23. Ewig S. Anamnese, klinische Symptomatik und Untersuchungsbefunde. In: Ewig S, editor. Ambulant erworbene Pneumonie. Bochum: Springer-Verlag Berlin Heidelberg; 2016. p. 67-70.
24. Ewig S, Bollow M. Diagnose. In: Ewig S, editor. Ambulant erworbene Pneumonie. Bochum, Deutschland: Springer-Verlag Berlin Heidelberg; 2016. p. 117-24.
25. Kolditz M, Ewig S. Community-Acquired Pneumonia in Adults. Dtsch Arztebl Int. 2017;114(49):838-48.
26. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.

27. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377-82.
28. Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. J Intern Med. 2006;260(1):93-101.
29. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243-50.
30. Kaysin A, Viera AJ. Community-Acquired Pneumonia in Adults: Diagnosis and Management. Am Fam Physician. 2016;94(9):698-706.
31. Ewig S, Bollow M. Radiologische Bildgebung. In: Ewig S, editor. Ambulant erworbene Pneumonie. Bochum: Springer-Verlag Berlin Heidelberg; 2016. p. 73-104.
32. Esayag Y, Nikitin I, Bar-Ziv J, Cytter R, Hadas-Halpern I, Zalut T, et al. Diagnostic value of chest radiographs in bedridden patients suspected of having pneumonia. Am J Med. 2010;123(1):88.e1-5.
33. Lee A, Mirrett S, Reller LB, Weinstein MP. Detection of bloodstream infections in adults: how many blood cultures are needed? J Clin Microbiol. 2007;45(11):3546-8.
34. Chaisuksant S, Koonsuwan A, Sawanyawisuth K. Appropriateness of obtaining blood cultures in patients with community acquired pneumonia. Southeast Asian J Trop Med Public Health. 2013;44(2):289-94.
35. Torres A, Cillóniz C, Ferrer M, Gabarrús A, Polverino E, Villegas S, et al. Bacteraemia and antibiotic-resistant pathogens in community acquired pneumonia: risk and prognosis. European Respiratory Journal. 2015;45(5):1353-63.
36. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67.
37. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect. 2011;17 Suppl 6(Suppl 6):E1-59.
38. Afshar N, Tabas J, Afshar K, Silbergleit R. Blood cultures for community-acquired pneumonia: are they worthy of two quality measures? A systematic review. J Hosp Med. 2009;4(2):112-23.

39. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. Respir Med. 2001;95(1):78-82.
40. Zhang D, Yang D, Makam AN. Utility of Blood Cultures in Pneumonia. Am J Med. 2019;132(10):1233-8.
41. Shimada T, Noguchi Y, Jackson JL, Miyashita J, Hayashino Y, Kamiya T, et al. Systematic review and metaanalysis: urinary antigen tests for Legionellosis. Chest. 2009;136(6):1576-85.
42. Del Rio-Pertuz G, Gutiérrez JF, Triana AJ, Molinares JL, Robledo-Solano AB, Meza JL, et al. Usefulness of sputum gram stain for etiologic diagnosis in community-acquired pneumonia: a systematic review and meta-analysis. BMC infectious diseases. 2019;19(1):403-.
43. Ogawa H, Kitsios GD, Iwata M, Terasawa T. Sputum Gram Stain for Bacterial Pathogen Diagnosis in Community-acquired Pneumonia: A Systematic Review and Bayesian Meta-analysis of Diagnostic Accuracy and Yield. Clin Infect Dis. 2020;71(3):499-513.
44. Rosón B, Carratalà J, Verdaguer R, Dorca J, Manresa F, Gudiol F. Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. Clin Infect Dis. 2000;31(4):869-74.
45. Anevlavis S, Petroglou N, Tzavaras A, Maltezos E, Pneumatikos I, Froudarakis M, et al. A prospective study of the diagnostic utility of sputum Gram stain in pneumonia. J Infect. 2009;59(2):83-9.
46. Fukuyama H, Yamashiro S, Kinjo K, Tamaki H, Kishaba T. Validation of sputum Gram stain for treatment of community-acquired pneumonia and healthcare-associated pneumonia: a prospective observational study. BMC Infect Dis. 2014;14:534.
47. Gatermann S. Streptokokken. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 198-214.
48. Vogel U, Elias J. Haemophilus. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 287-91.
49. Murdoch DR, Chambers ST. Atypical pneumonia--time to breathe new life into a useful term? Lancet Infect Dis. 2009;9(8):512-9.

50. Jacobs E. Mykoplasmen und Ureaplasmen. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 399-404.
51. Klos A. Chlamydien. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 405-15.
52. Pospisil L, Canderle J. Chlamydia (Chlamydophila) pneumoniae in animals: a review. VETERINARNI MEDICINA-PRAHA-. 2004;49(4):129-34.
53. Cunha BA. The atypical pneumonias: clinical diagnosis and importance. Clin Microbiol Infect. 2006;12 Suppl 3:12-24.
54. Kauppinen MT, Saikku P, Kujala P, Herva E, Syrjälä H. Clinical picture of community-acquired Chlamydia pneumoniae pneumonia requiring hospital treatment: a comparison between chlamydial and pneumococcal pneumonia. Thorax. 1996;51(2):185-9.
55. Pöhlmann S, Schmitt C. Orthomyxoviren: Influenza. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 476-81.
56. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011;377(9773):1264-75.
57. Gatermann S. Staphylokokken. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 187-97.
58. Bal AM, Gould IM. Antibiotic resistance in Staphylococcus aureus and its relevance in therapy. Expert Opin Pharmacother. 2005;6(13):2257-69.
59. Steinmetz I. Nichtfermentierende Bakterien (Nonfermenter): Pseudomonas, Burkholderia, Stenotrophomonas, Acinetobacter. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 265-74.
60. Restrepo MI, Babu BL, Reyes LF, Chalmers JD, Soni NJ, Sibila O, et al. Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. Eur Respir J. 2018;52(2).
61. Suerbaum S, Bockemühl J, Karch H. Enterobakterien. In: Suerbaum S, Hahn H, Burchard G-D, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 229-58.

62. Ashurst JV, Dawson A. Klebsiella Pneumonia. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2021, StatPearls Publishing LLC.; 2021.
63. Wasiński B. Extra-intestinal pathogenic Escherichia coli – threat connected with food-borne infections. Ann Agric Environ Med. 2019;26(4):532-7.
64. Ewig S, Kolditz M, Pletz M, Altiner A, Albrich W. Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie – Update 2021 2021 [Available from: https://www.awmf.org/uploads/tx_szleitlinien/020-020l_S3_Behandlung-von-erwachsenen-Patienten-mit-ambulant-erworbener-Pneumonie__2021-05.pdf.
65. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. Lancet (London, England). 2015;386(9998):1097-108.
66. Höffken G, Lorenz J, Kern W, Welte T, Bauer T, Dalhoff K, et al. [Epidemiology, diagnosis, antimicrobial therapy and management of community-acquired pneumonia and lower respiratory tract infections in adults. Guidelines of the Paul-Ehrlich-Society for Chemotherapy, the German Respiratory Society, the German Society for Infectiology and the Competence Network CAPNETZ Germany]. Pneumologie. 2009;63(10):e1-68.
67. Warming L. Qualitätsreport 2019 2019 [Available from: https://iqtig.org/downloads/berichte/2018/IQTIG_Qualitaetsreport-2019_2019-09-25.pdf.
68. Kolditz M, Tesch F, Mocke L, Höffken G, Ewig S, Schmitt J. Burden and risk factors of ambulatory or hospitalized CAP: A population based cohort study. Respir Med. 2016;121:32-8.
69. Schnoor M, Hedicke J, Dalhoff K, Raspe H, Schäfer T. Approaches to estimate the population-based incidence of community acquired pneumonia. J Infect. 2007;55(3):233-9.
70. Welte T, Marre R, Suttorp N. Was gibt es Neues in der Behandlung der ambulant erworbenen Pneumonie? Der Internist. 2006;101:313-20.
71. von Baum H, Welte T, Marre R, Suttorp N, Ewig S. Community-acquired pneumonia through Enterobacteriaceae and Pseudomonas aeruginosa: Diagnosis, incidence and predictors. Eur Respir J. 2010;35(3):598-605.
72. Forstner C, Rohde G, Rupp J, Schuette H, Ott SR, Hagel S, et al. Community-acquired Haemophilus influenzae pneumonia--New insights from the CAPNETZ study. J Infect. 2016;72(5):554-63.
73. Forstner C, Patchev V, Rohde G, Rupp J, Witzenrath M, Welte T, et al. Rate and Predictors of Bacteremia in Afebrile Community-Acquired Pneumonia. CHEST. 2020;157(3):529-39.

74. Partouche H, Lepoutre A, Vaure CBD, Poisson T, Toubiana L, Gilberg S. Incidence of all-cause adult community-acquired pneumonia in primary care settings in France. Med Mal Infect. 2018;48(6):389-95.
75. Laurichesse H, Robin F, Gerbaud L, Pochet P, Gourdon F, Beytout J, et al. Empirical therapy for nonhospitalized patients withcommunity-acquired pneumonia. European Respiratory Journal. 1998;11(1):73-8.
76. Leprince C, Desroches M, Emirian A, Coutureau C, Anais L, Fihman V, et al. Distribution and antimicrobial susceptibility of bacteria from adults with community-acquired pneumonia or complicated skin and soft tissue infections in France: the nationwide French PREMIUM study. Diagnostic Microbiology and Infectious Disease. 2015;83(2):175-82.
77. Glerant JC, Hellmuth D, Schmit JL, Ducroix JP, Jounieaux V. Utility of blood cultures in community-acquired pneumonia requiring hospitalization: influence of antibiotic treatment before admission. Respir Med. 1999;93(3):208-12.
78. Sterrantino C, Trifirò G, Lapi F, Pasqua A, Mazzaglia G, Piccinni C, et al. Burden of community-acquired pneumonia in Italian general practice. European Respiratory Journal. 2013;42(6):1739-42.
79. Viegi G, Pistelli R, Cazzola M, Falcone F, Cerveri I, Rossi A, et al. Epidemiological survey on incidence and treatment of community acquired pneumonia in Italy. Respiratory medicine. 2006;100(1):46-55.
80. Giorgi Rossi P, Agabiti N, Faustini A, Ancona C, Tancioni V, Forastiere F, et al. The burden of hospitalised pneumonia in Lazio, Italy, 1997-1999. Int J Tuberc Lung Dis. 2004;8(5):528-36.
81. Bonsignori F, Chiappini E, Orlandini E, Parretti A, Sollai S, Resti M, et al. Hospitalization rates of complicated pneumococcal community-acquired pneumonia is increasing in Tuscan children. Int J Immunopathol Pharmacol. 2013;26(4):995-1005.
82. Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One. 2013;8(9):e75131.
83. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. PROSPECTIVE STUDY OF THE AETIOLOGY AND OUTCOME OF PNEUMONIA IN THE COMMUNITY. The Lancet. 1987;329(8534):671-4.

84. Lim WS, Macfarlane JT, Boswell TCJ, Harrison TG, Rose D, Leinonen M, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax. 2001;56(4):296-301.
85. Rivero-Calle I, Pardo-Seco J, Aldaz P, Vargas DA, Mascarós E, Redondo E, et al. Incidence and risk factor prevalence of community-acquired pneumonia in adults in primary care in Spain (NEUMO-ES-RISK project). BMC Infectious Diseases. 2016;16(1):645.
86. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F. Epidemiology of community-acquired pneumonia in older adults: a population-based study. Respir Med. 2009;103(2):309-16.
87. Ochoa-Gondar O, Vila-Córcoles A, de Diego C, Arija V, Maxenchs M, Grive M, et al. The burden of community-acquired pneumonia in the elderly: the Spanish EVAN-65 study. BMC Public Health. 2008;8:222.
88. Gutiérrez F, Masiá M, Mirete C, Soldán B, Rodríguez JC, Padilla S, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect. 2006;53(3):166-74.
89. Almirall J, Bolibar I, Vidal J, Sauca G, Coll P, Niklasson B, et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. European respiratory journal. 2000;15(4):757-63.
90. Zalacain R, Torres A, Celis R, Blanquer J, Aspa J, Esteban L, et al. Community-acquired pneumonia in the elderly: Spanish multicentre study. Eur Respir J. 2003;21(2):294-302.
91. Cillóniz C, Ewig S, Polverino E, Marcos MA, Esquinas C, Gabarrús A, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax. 2011;66(4):340-6.
92. Cillóniz C, Gabarrús A, Almirall J, Amaro R, Rinaudo M, Travierso C, et al. Bacteraemia in outpatients with community-acquired pneumonia. European Respiratory Journal. 2016;47(2):654-7.
93. Falguera M, Trujillano J, Caro S, Menéndez R, Carratalà J, Ruiz-González A, et al. A Prediction Rule for Estimating the Risk of Bacteremia in Patients with Community-Acquired Pneumonia. Clinical Infectious Diseases. 2009;49(3):409-16.
94. Naucler P, Henriques-Normark B, Hedlund J, Galanis I, Granath F, Örtqvist Å. The changing epidemiology of community-acquired pneumonia: nationwide register-based study in Sweden. J Intern Med. 2019;286(6):689-701.

95. Holmberg H. Aetiology of community-acquired pneumonia in hospital treated patients. Scand J Infect Dis. 1987;19(5):491-501.
96. Lagerström F, Bader M, Foldevi M, Fredlund H, Nordin-Olsson I, Holmberg H. Microbiological etiology in clinically diagnosed community-acquired pneumonia in primary care in Orebro, Sweden. Clin Microbiol Infect. 2003;9(7):645-52.